MODELLING LONGITUDINAL CHILD GROWTH DATA IN AFRICAN SETTINGS

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A Thesis submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in fulfilment for requirements for a degree of Doctor of Philosophy (by publication).

Johannesburg, 2015

CANDIDATE DECLARATION

I declare that this thesis is my own unaided work. It is being submitted for a degree of Doctor of Philosophy in the University of Witwatersrand, Johannesburg. It has not been submitted for any degree or examination at any other University or institution.

17 July 2015

Esnat D. Chirwa Date

DEDICATION

This thesis is dedicated to my wonderful children, Temweka and Thumbiko, my husband and friend, Tobias, my wonderful father, Evaristo, and my late mother, Justina. I am deeply grateful for your love and support.

THESIS MATERIAL

Over the course of this PhD, the research was written up and published as a series of Paper publications. The results were also presented at various conferences and seminars.

Publications

1. Chirwa ED, Griffiths PL, Maleta K, Norris SA, Cameron N. Multi-level modelling of longitudinal child growth data from the Birth-to-Twenty Cohort: a comparison of growth models. ***Annals of Human Biology. 2014 Mar; 41(2):166-177.***

   Contributions:

   PhD student: Responsible for conceptualisation of the manuscript which involved defining the objectives and methodology to be used, performing data management (including data cleaning, coding and manipulation), data analysis (modelling and performing model diagnostics) and was responsible for drafting the manuscript, submission of the manuscript to the journal and responding to reviewers' comments.

   Co-authors: Provided guidance on the conceptualisation of the objectives, editing of the manuscripts and/or reviewing of the manuscript drafts.

2. Chirwa E.D, Griffiths PL, Maleta K, Ashorn P, Pettifor J.M, Norris S.A. Postnatal growth velocity and overweight in early adolescents: A comparison of rural and urban African boys and girls. ***American Journal of Human Biology. 2014 Jun; 26(5): 643-651.***

Contributions:

PhD student: Responsible for conceptualisation of the manuscript which involved literature review, defining manuscript objectives and methodology (statistical methods) to be used, performing data management (data cleaning, data coding and manipulation), data analysis (data simulations and modelling, and performing model diagnostics). The student was also responsible for drafting the manuscript, submission of the manuscript to the journal and responding to reviewers' comments.

Co-authors: Provided guidance on the conceptualisation, editing of the manuscripts and/or reviewing of the manuscript drafts.

3. Chirwa ED, Griffiths P, Norris SA, Maleta K, Ashorn P, Cameron N. Intermittent missing measurements in physical growth of children: Is it necessary to impute? (*BMC Medical Research Methodology - under review*)

Contributions:

PhD student: Responsible for conceptualisation of the manuscript which involved defining the objectives and methodology to be used. The student performed data management (including data cleaning, coding and manipulation) and data analysis (modelling and performing model diagnostics). The student was also responsible for drafting the manuscript and submission of the manuscript to the journal.

Co-authors: Provided guidance on the conceptualisation of the objectives, editing of the manuscripts and/or reviewing of the manuscript drafts.

Conference and Seminar proceedings

1. Oral Presentation: Chirwa ED, Norris SA, Maleta K, Griffiths P; Intermittent missing measurements in physical growth of children: Is it necessary to impute? Presented at the Cross-Faculty Postgraduate Symposium, University of Witwatersrand, August 2013.

2. Oral Presentation: Chirwa E.D, Griffiths P, Maleta K, Norris S.A. Postnatal growth velocity and overweight in early adolescents: A comparison of rural and urban African boys and girls (Preliminary results). Presented at the CARTA Joint Advanced Seminar III, August 2013, University of Ibadan, Nigeria.

3. Poster Presentation: Chirwa ED, Norris SA, Maleta K, Griffiths P. Intermittent missing measurements in physical growth of children: Is it necessary to impute? Presented at the 2013 Public Health Association of South Africa (PHASA) conference, September 2013, Cape Town, SA.

Awards:

1) Consortium for Advanced Research Training in Africa (CARTA) [†] Research Training fellowship (2011-2014).
2) CARTA Travel grant for PHASA (2013) Conference.
3) Fogarty Scholarship to attend a short course on 'Statistical Methods for Missing Data & Causal Inference' in Kenya (2014).

[†]The Consortium for Advanced Research Training in Africa (CARTA) is jointly led by the African Population and Health Research Centre and the University of the Witwatersrand and funded by the Welcome Trust (UK) (Grant no: 087547/Z/08/Z), the Department for International Development (DfID) under the Development Partnerships in Higher Education (DelPHE), the Carnegie Corporation of New York (Grant no: B 8606), the Ford Foundation (Grant no: 1100-0399), Google. Org (Grant no: 191994), SIDA (Grant no: 54100029) and MacArthur Foundation (Grant no: 10-95915-000-INP).

ABSTRACT

Rationale: With more and more studies in human and biological sciences involving longitudinal, multi-level or hierarchical data, skills in manipulation and analysis of such data have become very essential in understanding public health problems and in guiding public health policy. Longitudinal child growth studies are particularly useful in monitoring child growth and understanding relationships between early childhood growth and later life health outcomes. However, one of the challenges of longitudinal studies is the inevitability of missing data due to missed visits or lost to follow up. Use of appropriate statistical methods that deal with missing data in longitudinal physical growth measurements and also take into account the correlations in measurements is thus very essential in understanding these relationships.

Aims: The main aims of the thesis were to apply mixed effects modelling and various advanced statistical methodologies to longitudinal physical growth data from 2 African growth cohorts in order to: identify biological growth curves that best fit childhood physical growth measurements in these African settings, identify statistical methods that efficiently deal with missing data in physical growth measurements and, then explore the relationship between postnatal growth velocity and early adolescent obesity in the 2 cohorts.

Methods: The study used physical growth measurements from the Birth to Twenty (BT20 - an urban South African cohort) and from the Lungwena Child Survival Study (a rural cohort from Malawi). There were differences in the intensity of the data collection waves in the 2 cohorts. Several parametric and non-parametric growth curves were fitted to height and weight measurements from birth to 10 years, using Linear Mixed Effects (LME) modelling. Both cohorts were modelled from birth to around 10/11 years. However, there were shorter intervals between data collection waves in the Lungwena than the BT20 cohort. Several goodness of fit statistics were used to compare how well the different curves fitted to the data. The parameter

estimates of the Berkey-Reed model , which was found to fit better to the data than the other models, were then used to compare the efficiency of using Multiple Imputation, Regression Imputation or using available case analysis (ACA) methods to deal with missing growth data. The study used LME models as an ACA method. Lastly, the study further used LME models to derive growth velocity curves and then used logistic and multiple linear regression models to explore the relationship between postnatal growth and adolescent obesity.

Results:

Identification of growth curves:

In comparing how the different human growth models fitted to the 2 cohorts, the study found that the Berkey-Reed 1st order model fitted well to both weight and height measurements in both cohorts compared to other growth models. Overall, the fitness of different models was affected by length of time between data collection waves, especially in the first year of life, as evidenced by smaller residuals in the Lungwena cohort, which had data points that were closer together than the BT20 cohort. There was improved model fit when there were more data points in early years (birth to 2 years), because this allowed for better capturing of the expected. The number of data points in early years also affected predictions of initial weight/length (birth weight/length) by the models, as evidenced by better prediction in the Lungwena cohort.

There were also variations in precision of the estimated initial weight or height by the different models. In general, most models failed to pick out the pre-puberty rapid growth (at 7-9 years). Overall, there was better fit to height measurements than weight measurements due to the monotonic nature of height measurements. Human growth models are monotonic functions, primarily derived to model monotonic biological processes. However, individual weight

fluctuates and is more sensitive to changes in ecological and environmental factors that affect growth.

Dealing with missing physical growth measurements

In comparing methods of dealing with missing data in longitudinal studies, the study found that there were no significant differences in the growth model parameter estimates derived after MI or using regression imputation or when using LME modelling, which uses all available information. However the efficiency of MI or LME was affected by the length of the period between data collection waves. Bias in the estimated parameters was consistently affected by the number of data points (amount of information from each child), with the Lungwena cohort parameters having reduced bias because of the larger number of data points.

There was also more bias in MI values if imputation model used did not take into account the individual child's growth profile (i.e. the longitudinal aspect of the data). The regression imputation method produced smaller standard errors than the ACA-based LME method, due to the increased number of observations created through the imputation process.

Relationship between infant growth and early adolescent obesity

Having found no significant gain in using Multiple Imputation or regression imputation in growth curve modelling, the study used LME modelling (which allows for missing data) to examine the relationship between early child growth and adolescent obesity. LME is simple to use in growth curve modelling, especially in deriving other growth parameters such as peak weight/height velocities or time at peak velocity. The study found that there were significant differences in growth between the 2 cohorts, shown by the differences in the growth model parameters and weight/height growth velocities. BT20 boys and girls exhibited higher growth

rates than their Lungwena counterparts. The differences between the 2 cohorts were also highlighted by the changes in relationships between growth parameters when models were adjusted for inherent cohort differences. However, no significant differences were observed between boys and girls within each cohort.

No significant relationship was found between size at birth (birth weight) and adolescent obesity, even after taking into account inherent cohort differences. Rapid growth in infancy, independent of size at birth (birth weight) was highly associated with high BMI in early adolescent. In general, the risk of being an overweight adolescent increased with increase in growth velocity. The relationship between growth velocity and adolescent body mass index (BMI) was strongest for infant rather than childhood growth velocity.

There was a general decrease in the strength of the relationship between weight velocity and adolescent BMIZ over time even after adjusting for birth weight, with the strongest relationship observed in infancy. Adolescent obesity was also associated with age at peak velocity, with infant that reached peak velocity early having higher risk of being obese in adolescence.

Conclusions:

Shorter intervals between data collection waves in the first 24 months of life (a period of general rapid growth) will lead to better fit of the growth models. Thus, for optimal study of infant and early childhood growth using these types of growth models, it is recommended to have measurements at least every 3 months.

There is no gain in using MI or Regression Imputation in dealing with intermittent missing data in physical growth measurements in early childhood (birth to 10 years), especially if the time

intervals between data collection waves are short. Available Case Analysis using LME method can produce sufficient and unbiased results. The method allows for analysis of unbalanced repeated measures that might arise by study design or due to missing data and is also simpler to use than MI. Regression Imputation, which also uses LME method to predict values, has the advantage of increasing the number of observations used, and thus helps in increasing the precision of the parameter estimates (reduced standard errors).

Overall, rapid weight gain in infancy is highly associated with adolescent obesity. However the effect of rapid growth can have different health outcomes depending on what stage of nutritional transition the population is in. For a rural population that is still in the early stages of nutritional transition, rapid weight gain in infancy may have beneficial effects as it protects an adolescent child from the effects of under-nutrition, with children who experience rapid growth having reduced risk of stunting and under-weight. For an urban population in later stages of nutritional transition, rapid weight gain in infancy has detrimental effects, which exacerbates the effects of adolescent over-nutrition, thus increasing the risks of adolescent obesity.

The study highlighted the diversity in nutritional problems that exist in Africa as a continent and the need to understand each country in terms of stage of nutritional transition, when designing public health interventions and also how other countries in the continent can learn from South Africa in mitigating the effects of over-nutrition.

ACKNOWLEDGEMENTS

This has been a challenging but rewarding experience. I would therefore wish to extend my sincere appreciation to my colleagues, family and friends who have supported me over the course of this journey. In particular, I am most grateful to the following people without whose assistance, guidance, advice and encouragement this would not have been possible.

I wish to thank Professor Shane Norris for agreeing to serve as my main supervisor, for providing the data which provided real life challenges for my statistical ideas for this PhD and for assisting with the conceptualisation of the study. His continued support (intellectually and financially) throughout the PhD is greatly appreciated.

I wish to thank Professor Ken Maleta for support and guidance, and for the provision of supplementary data that made my PhD study both challenging and interesting.

To Dr Paula Griffiths, I am thankful for your guidance, encouragement and for reviewing of the statistical aspects of the study. I am sincerely grateful for generously giving your time to look at my work, no matter how busy you were.

I extend my sincere gratitude to Prof Per Ashorn (University of Tampere, Norway), Prof John Pettifor (University of Witwatersrand), and Prof Noel Cameron (University of Loughborough). Their insightful, thought-provoking questions and comments on the drafts of the PhD publications have been invaluable.

Thank you to the Birth to Twenty cohort and Lungwena children and families for their participation in the projects.

I am grateful to the Consortium for Advanced Research Training in Africa (CARTA) for the fellowship which provided financial and training support for my PhD study.

My CARTA Cohort 1 colleagues, thank you for the friendship, encouragement and the fun we shared. Finally, to my family: my husband Tobias, for your encouragement and support, my kids (Temweka and Thumbiko), for enduring my long absence from home, and my dad, for your words of support and encouragement.

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List of Abbreviations

ACA : Available Case Analysis

BH : Bone Health

BMI : Body mass index

BT20 : Birth to Twenty

CCA : Complete Case Analysis

DOAHaD : Developmental Origins of Adult Health and Disease

GEE : Generalised Estimating Equations

GLM : General Linear Models

HAZ : Height-for-age z-scores

LBW : Low Birth weight

LCSS : Lungwena Child Survival Study

LME : Linear Mixed Models

LMIC : Low and Middle Income Country

LOCF : Last Observation Carried Forward

MANOVA : Multivariate Analysis of Variance

MAR : Missing at random

MCAR : Missing completely at random

MCMC : Markov Chain Monte Carlo

MI : Multiple Imputations

MNAR : Missing not at random

NCD : Non-Communicable Disease

NCHS : National Centre for Health Statistics

NLME : Non Linear Mixed Models

PCA : Principal Component Analysis

PHV : Peak height velocity

PWV : Peak weight velocity

REM : Random Effects Models

SES : Socio-Economic Status

WAZ : Weight-for-age z-scores

WHO : World Health Organisation

WHZ : weight-for-height z-scores

PREFACE

My interest in applied statistics for biological sciences goes back to the experiences during my Postgraduate Diploma in Statistics and Masters in Biometry at the University of Reading. The programme had a diverse curriculum, with applications in health sciences, agriculture and environmental sciences. My undergraduate background is in Computer Science and Statistics done at the University of Malawi. However, I have been more interested in Statistics and have used my computing knowledge to enhance my statistical skills. The experience I gained during my research for the Masters programme motivated me to further my career as a Biostatistician. And indeed, in between teaching statistics to undergraduate students at the University of Malawi, I was also involved in teaching and supervising postgraduate students in Biological and Environmental Sciences. Despite having a postgraduate degree in Statistics, I felt the desire to deepen my knowledge of the different statistical methods and to experience the challenges in the application of the different methods to real data. The other motivating factor was the option of doing a PhD by publication. Apart from deepening my statistical skills and knowledge, doing a PhD by publication allowed me to learn research and publication skills.

My research interests include the application of statistical modelling to public health research, with particular interest in statistical methods for analysing longitudinal or hierarchical data as well as in those that deal with missing data.

Longitudinal studies, though expensive and time consuming, are very important in understanding public health problems, and use of appropriate statistical methods in the analysis of such data is essential in guiding health policy development. Thus the opportunity to analyse child growth data from the Birth to Twenty (BT20), a child cohort from urban South Africa

and Lungwena Child Survival Study (LCSS), a cohort from rural Malawi, posed interesting challenges not to be surpassed, both methodologically and empirically.

The main challenge in the BT 20 cohort was the missing anthropometric measurements in the first year of life. This posed a limitation to the researchers interested in exploring the relationship between early childhood growth and adolescent or adult health outcomes. The difference between LCSS and BT20, in terms of the intensity of the data collection and the amount of missing data posed a perfect platform for exploring methodologically issues of missing data in repeated physical growth studies that could not be missed. The contextual differences (rural and under-nutrition versus urban and its dual burden of over and under nutrition) in the 2 cohorts provided an empirical opportunity for me to add knowledge to the field of developmental origins of adult diseases and explore using Linear mixed effects (LME) modelling the relationship between early childhood growth and adolescent obesity.

However, to be able to answer the empirical question of the relationship between postnatal growth and adolescent obesity, it was necessary to deal with the statistical challenges posed by missing measurements as well as the correlation between individual child's measurements. Thus before I could look at the relationship between postnatal growth and adolescent obesity, it was necessary to find an optimum method of dealing with the missing measurements in the data using each child's growth profile.

PART 1: RELEVANT BACKGROUND

Part 1 of the thesis consists of 2 chapters. Chapter 1 gives a brief introduction, justification of the study and an overall study overview. Chapter 2 deals with the existing background literature for the statistical and biological components of the study, and outlines the aims and objectives of the PhD study.

CHAPTER 1 : INTRODUCTION

This thesis examines the childhood growth profiles of children from different African settings, an urban cohort from a middle income country and a rural cohort from a low income country. It sets out to examine the relationship between postnatal early childhood growth and obesity in early adolescence and use advanced temporal statistical methods to deal with the challenges of longitudinal data.

1.1 JUSTIFICATION OF THE STUDY

The following section deals with the justification of the study which begins with a discussion on the importance of longitudinal child growth studies in Low and Middle Income Countries, where such studies are limited. The justification then highlights the challenges in analysis of data from longitudinal studies in general and longitudinal child growth studies in particular.

1.1.1 Limited data from child growth studies and value of longitudinal studies.

Longitudinal child growth studies are useful in monitoring child growth and understanding the relationship between early childhood growth and later life health outcomes. There is substantial literature that supports the hypothesis that adult health status has origins in early life (Adair et al., 2009, Barker et al., 2010, Demerath et al., 2009, Ekelund et al., 2007, Eriksson et al., 2000, Eriksson et al., 2001, Kimani-Murage et al., 2010, Stein et al., 2010) . Longitudinal studies in developed countries have shown that rapid growth in infancy is associated with adolescent and adulthood obesity and other diseases of lifestyle (Ekelund et al., 2007, Eriksson et al., 2007, Stein et al., 2010). These studies have shown that the risk of certain chronic diseases such as Type 2 diabetes, hypertension and other related risk factors are increased in individuals that had small birth weight but who are relatively large in adulthood (Ekelund et al., 2007, Elks et al., 2010, Eriksson and Forsen, 2002, Eriksson et al., 2003).

However, some studies in low income countries have shown that catch-up growth for low birth weight (LBW) infants is desirable as LBW infants who exhibited catch up growth had reduced child morbidity and mortality rates (Kalanda et al., 2005a, Victora et al., 2001). Several other

studies have shown the benefits (Vaahtera et al., 2000, Victora et al., 2001, Maleta et al., 2004, Kalanda et al., 2005b) and detrimental effects (Crowther et al., 1998, Eriksson et al., 2000, Eriksson et al., 2001, Cameron et al., 2003, Ekelund et al., 2007, Eriksson et al., 2007, Adair et al., 2009) of infant rapid weight gain.

Several studies have looked at child growth in low-and middle-income countries, but few have used longitudinal data, due to the limited number of longitudinal studies (Adair et al., 2009, Fetuga et al., 2011, Guedes et al., 2010, Hauspie and Pagezy, 1989, Johnson et al., 2012b, Kalanda et al., 2005b, Maleta et al., 2003a, Maleta et al., 2003b, Mushtaq et al., 2012, Nguyen et al., 2012, Olusanya and Renner, 2011, Pagezy and Hauspie, 1985, Simondon et al., 1992, Stein et al., 2010).

Longitudinal studies are generally labour intensive, time consuming and expensive. This has resulted in a limited number of child cohort studies in developing countries, especially in Sub-Saharan Africa. At the same time, most LMICs are going through different stages of nutritional transition and are now being faced with two extremes of malnutrition (under-nutrition and over-nutrition), due to differences in nutritional transition between rural and urban areas, creating a 'double burden' of malnutrition (Subramanian et al., 2007, Corsi et al., 2011, Griffiths and Bentley, 2001, Popkin, 1998, Popkin, 2001).

Most low income countries have concentrated their programmes on dealing with under nutrition. Programmes to look at the life course interventions are all aligned with dealing with under-nutrition and do not consider the detrimental effects of rapid weight gain. However, with most LMICs undergoing nutritional transition due changes in lifestyle between rural and urban settings, the co-existence of over-nutrition and under-nutrition needs to be taken into account. It would thus be prudent under the changing circumstances to consider the detrimental long-

term effects of rapid infant growth, and programmes that raise awareness of the emerging health problem.

Thus, longitudinal child growth studies are essential in the developing countries for informing public health policies in the mitigation of the short and long term effects of this double-burden of malnutrition. It is therefore very important to utilise the available, albeit limited longitudinal studies, in understanding the relationship between postnatal growth and, later, adolescent and adult health outcomes in this particular population setting.

1.1.2 Statistical methodological challenges of longitudinal studies.

The main challenges in the analysis of longitudinal studies are the inevitability of missing data and the correlation of measurements within an individual. Missing data can arise due to missed visits, drop out, or loss to follow up, amongst other reasons. Traditional regression techniques such as Generalised Linear Models (GLM) are based on the assumption that observation units are independent (Goldstein et al., 2002). Use of such methods to understand biological phenomena (such as animal growth) may lead to over-estimation of measures of effects because measurements are often clustered within individuals.

Apart from issues of correlation of measurements, most traditional statistical methods for analysing longitudinal data such as Multivariate Analysis of Variance (MANOVA) require individuals to have the same number of measurements and assume that the measurements are taken at the same time. The presence of missing data in longitudinal studies thus creates an imbalance in the number of measurements. Use of methods such as MANOVA would require

removing all participants with some missing measurements. This can lead to substantial reduction in sample size. Thus, appropriate statistical methods that deal with missing data as well as the correlation in the repeated measurements are essential. Such methods include mixed effects models, which are flexible in dealing with unbalanced longitudinal data created by either missing data or design of study. Another option in dealing with missing data in longitudinal studies is to impute for the missing information, using different imputation methods such as Multiple Imputation, regression imputation and mean imputation. Studies have either used mixed effect modelling or have imputed for missing data (McCarthy et al., 2007, Botton et al., 2008, Li et al., 2003, Wen et al., 2012). However, very few studies have compared the performance of these different methods of dealing with missing data, especially in physical growth measurements (Peters et al., 2012, Tang et al., 2005, Twisk and de Vente, 2002).

Thus, with more and more studies in human and biological sciences involving longitudinal, multi-level or hierarchical data, skills in manipulation and analysis of such data are very essential in understanding problems in public health and guiding health policy (Nsubuga et al., 2006, Pisani and AbouZahr, 2010).

1.1.3 Methodological challenges in the analysis of longitudinal physical growth measurements.

To examine the relationship between adolescent obesity and infant or early childhood growth, several methodological issues need to be addressed. These will be considered in greater detail in later chapters of the thesis. Figure 1.1 below summaries issues involved in the modelling of longitudinal physical growth measurements.

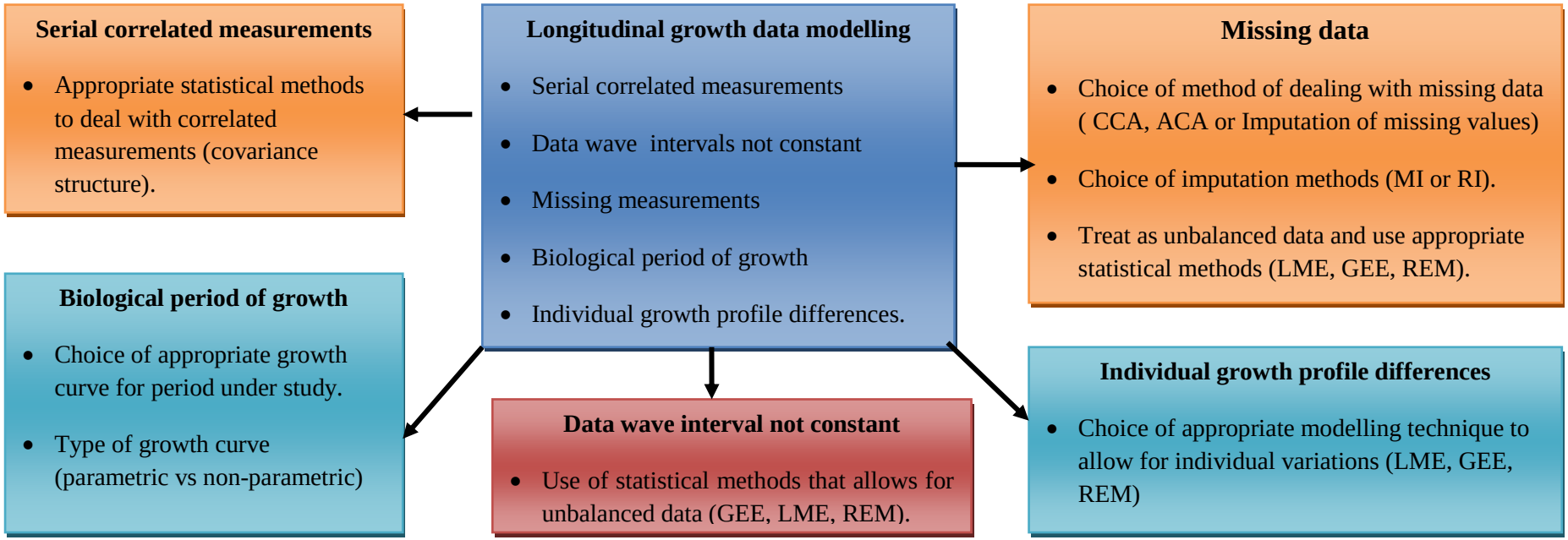


Figure 1.1 Methodological challenges of modelling longitudinal physical growth data.

GEE: General Estimating Equation. MI: Multiple Imputations. RI: Regression Imputation. CCA: Complete Case Analysis
LME: Linear Mixed Effects Modelling. REM: Random Effects Modelling. ACA: Available Case Analysis.

1.2 THESIS OVERVIEW

The diagram (Fig 1.2) below summarises the general empirical motivation for the PhD study and shows a summary of relationships between pre-and post natal growth and adolescent obesity and factors associated with growth at different periods (Wells et al., 2007, McCarthy et al., 2007)[1].

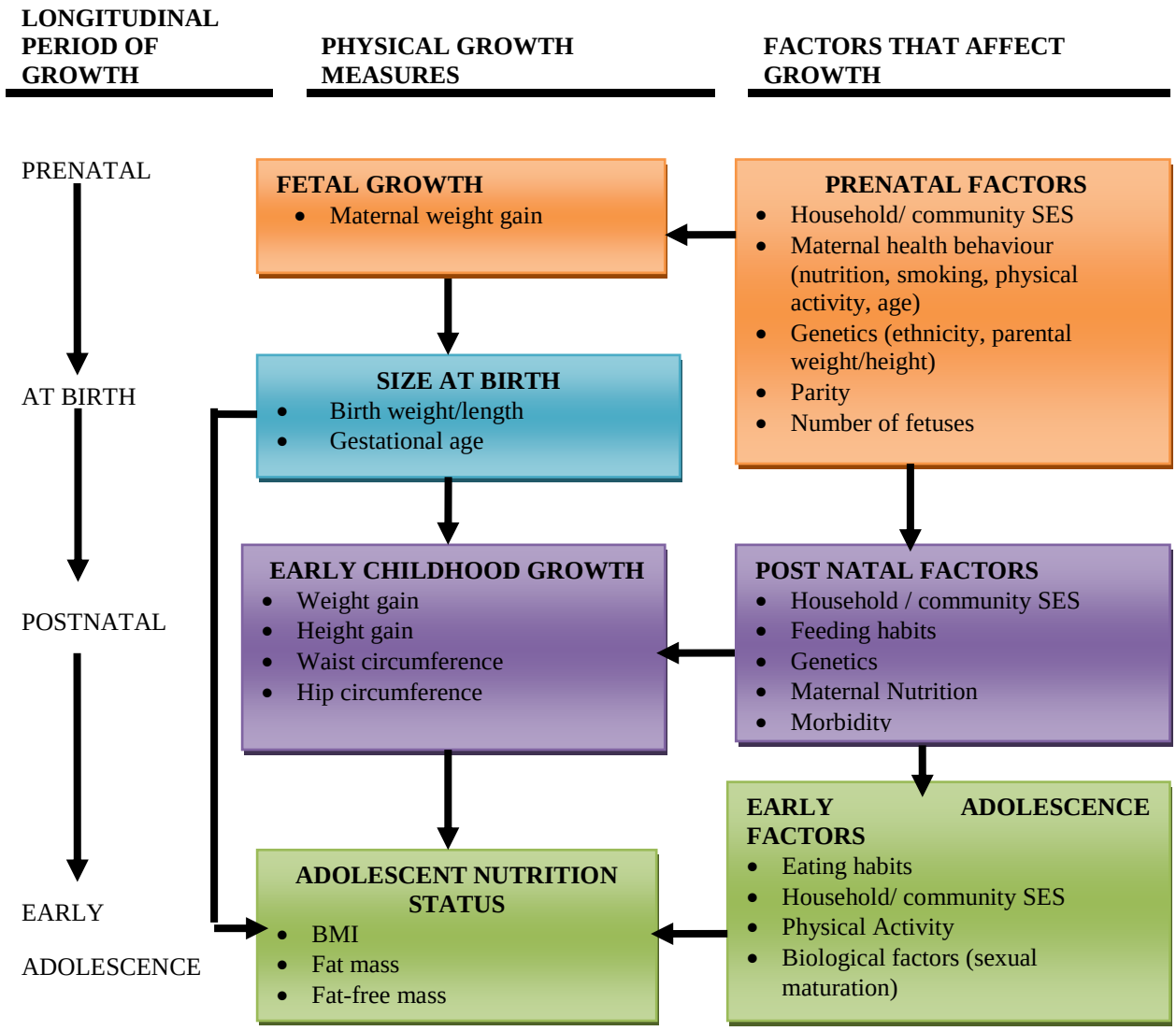


Figure 1.2 Factors associated with early childhood growth and adolescent obesity.

[1] The diagram is based on ideas from these references.

1.3 AIMS AND OBJECTIVES

The broad aim of the PhD study was to examine the relationship between early postnatal growth and obesity in early adolescence. To achieve this broad aim, the following objectives were derived:

1. To explore childhood growth curves that best describe infant and childhood growth in 2 African settings.
2. To compare statistical methods of dealing with missing data in longitudinal physical growth measurements.
3. To compare growth of children in rural and urban African settings.
4. To examine the relationship between early childhood growth and early adolescent obesity.

The specific objectives from each of the broad objectives were as follows:

1. For exploring childhood growth curves that best describe infant and childhood growth in 2 African settings:
    - Compare the fit of different parametric and non-parametric childhood growth models.
    - Assess the effect of time interval between data collection waves on model fit.
2. For comparing statistical methods of dealing with missing data in longitudinal physical growth measurements:

- To assess the efficiency of the Available Case Analysis (ACA) method in dealing with missing data.
- To assess the added value of Multiple Imputation (MI) in the analysis of missing physical growth data.
- To assess the added value of growth model-based interpolation in the analysis of missing physical growth data.
- To assess the effect of time interval between data collection waves on the reliability and precision of the different methods of dealing with missing data.

3. For comparing growth of children in rural and urban African setting:
   - To compare infant growth velocity in the 2 different settings.
   - To compare prevalence of early adolescent obesity in the 2 settings.

4. For examining the relationship between early growth and early adolescent obesity:
   - To examine the relationship between infant and early childhood growth velocity, and early adolescent BMI.
   - To examine the association between early adolescent obesity and infant growth rates.

CHAPTER 2: LITERATURE REVIEW

This chapter outlines the background literature review that motivated the PhD study. The review looks at the biology of human physical growth, the statistical methods and challenges associated with modelling of human growth. The first part of this chapter describes human physical growth and models used to describe physical growth in children. The chapter then reviews statistical methods used in dealing with correlated longitudinal measurements and methods used in dealing with missing data in longitudinal measurements.

2.1 HUMAN GROWTH

Human growth, like most developmental processes is complex, but can broadly be classified into two main phases:-prenatal/ uterine growth and postnatal growth. Cameron, further defines postnatal growth into three phases namely infancy, childhood and adolescence and most individuals will experience some rapid growth (growth spurts) in each of the three phases (Cameron and Demerath, 2002, Hauspie et al., 2004). Human growth is affected by a number of factors, ranging from genetic/biological to behavioural and environmental. Environmental factors include household socioeconomic status, access to health care, community services and infrastructure, economic development of a community, and disease environment among others, while behavioural factors include dietary habits, physical activity, cultural and religious beliefs, child care practices, and health care practices (Cameron, 1997, Cameron, 2007, Cunha et al., 2010, Griffiths et al., 2008, Karaolis-Danckert et al., 2009).

2.1.1 Prenatal growth

There is substantial literature that supports the hypothesis that adult health status has its origins in early life (Adair et al., 2009, Barker et al., 2010, Demerath et al., 2009, Ekelund et al., 2007, Eriksson et al., 2000, Eriksson et al., 2001, Kimani-Murage et al., 2010, Stein et al., 2010). These studies have looked at the association between birth weight, which is a proxy measure for foetal (uterine) growth, and some of the adult non-communicable diseases (NCDs). Foetal growth is affected by several factors such as maternal nutrition and diseases, and impaired placental function, among others. Low birth weight, which is an indication of retarded growth of the foetus, has been shown to be directly associated with poor neonatal outcomes, including infant mortality and morbidity (Kalanda et al., 2005a). The ‘developmental origins of adult

disease and health' (DOADaH) hypothesis (also referred to as the foetal programming hypothesis) was proposed to explain the observed associations between low birth weight and a range of non-communicable adult diseases such as hypertension, diabetes and obesity (Barker et al., 2010, Forsen et al., 2000, Tu et al., 2007). These associations have been interpreted as evidence that foetal growth retardation has adverse long-term effects on the development of vital organ systems, which predispose the individual to a range of metabolic and related disorders in later life (Tu et al., 2007). It has also been shown to be associated with changes in the shape of the kidneys, a reduction in the kidney volume and fewer nephrons (Eriksson et al., 2007). Thus, monitoring child growth from the foetal stage is important in understanding adulthood non-communicable diseases. Birth weight, which has been used as proxy measure for foetal growth is an important variable in understanding this association. Many studies have used birth weight as proxy for foetal growth due to the costly nature of specialised equipment that can monitor and measure foetal growth.

2.1.2 Postnatal growth

Cameron (Cameron and Demerath, 2002), defines postnatal growth into three phases namely infancy, childhood and adolescence and most individuals will experience some rapid growth (growth spurts) in each of the three phases. Postnatal human physical growth is generally characterised by rapid growth in early life, followed by a general deceleration in childhood and then a marked increase in growth in late childhood associated with the onset of puberty (Goldstein and Pan, 1998, Grimm et al., 2011, Karlberg, 1987). Irrespective of birth weight, between 6-18 months, children undergo rapid growth. However, this rapid weight gain has the potential to be more pronounced in children with low birth weight than in the other categories

and has been referred to as an ‘adaptation from intrauterine to extra uterine growth’ (Gasser and Molinari, 2004).

Several studies have shown the benefits (Victora et al., 2001, Maleta et al., 2004, Kalanda et al., 2005b) and detrimental effects (Crowther et al., 1998, Eriksson et al., 2000, Eriksson et al., 2001, Cameron et al., 2003, Ekelund et al., 2007, Eriksson et al., 2007, Adair et al., 2009) of infant rapid weight gain.

These studies have shown that children with low birth weight are more likely to become obese in adolescence if they exhibited rapid weight gain in their first year of life (Eriksson et al., 2001, Cameron et al., 2005). Other studies have investigated the association between childhood growth and health status in adulthood (Ekelund et al., 2007, Eriksson et al., 2007, Stein et al., 2010, Adair et al., 2009). These studies have shown that the risk of certain chronic diseases such as Type 2 diabetes, hypertension and other related risk factors are increased in individuals that had small birth weight but who are relatively large in adulthood (Crowther et al., 2008, Cameron et al., 2003, Crowther et al., 1998, Eriksson et al., 2001).

On the other hand, in low income countries like Malawi with low levels of prevalence of overweight and obesity, catch-up growth for LBW is desirable, as studies have shown that LBW infants who exhibit catch up growth have reduced child morbidity and mortality rates in such environments (Victora et al., 2001, Kalanda et al., 2005b). However, these studies have not monitored the impact of such growth into adolescence, so as to examine the long-term effect of such catch-up growth into adulthood.

2.1.3 Child Growth modelling

Statistical models are mathematical representations of the population behaviour, and describe the important characteristics of the hypothesized process of interest among individuals in the target population (Singer and Willett, 2003). By using a particular growth curve, one implicitly indicates that the particular population process gave rise to the sample data observed. The models are thus defined using parameters that represent population quantities of interest and the sample data provides the evidence or otherwise for the hypothesized population model. Similarly, human growth models are mathematical representations of the human growth process, and model parameters in human growth curves represent particular milestones in the human growth process (Hauspie et al., 2004).

Thus, statistical modelling of human growth involves fitting the hypothesized human growth process to the sample data and then estimating the population parameters of interest. Since the modelling process seeks to estimate the unknown but hypothesized population milestones, methods of estimation must provide some measure of how well the sample data is fitting to the hypothesized process.

Growth curve models have been used in various disciplines to understand and capture general features of growth processes. They have extensively been used in developmental research to understand biological as well as psychological processes at the individual or population level, using data collected longitudinally (Black and Krishnakumar, 1999, Botton et al., 2008, Ehrenkranz et al., 1999, Grimm et al., 2011, Nguyen et al., 2012, Olusanya and Renner, 2011, Skinner et al., 2004). Modelling of such longitudinal growth data involves fitting a model or curve that best describes the changes in the growth measurements of an individual or population over time (Goldstein and Pan, 1998, Steele, 2008). The rationale behind population-

based growth curve modelling is that while different individuals are different in terms of their initial birth measurements and their growth rates, their general growth over time follow similar pattern/shape. Thus, the fitted models can then be used to summarize and interpolate the pattern of growth in between measurement occasions and also identify critical periods in the growth process (Hauspie et al., 2004). Considering the non-linearity of the human growth process, especially in early childhood, a good human growth model should be able to capture the non-linear developmental patterns in individual growth.

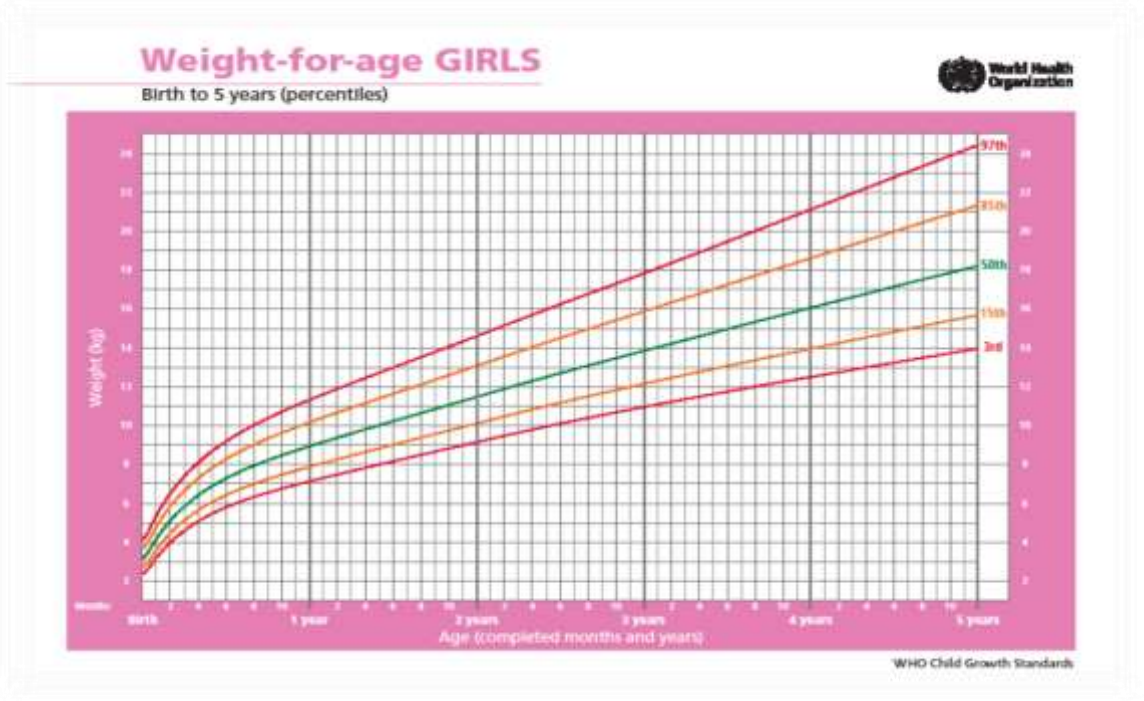
Over the years researchers have used different growth models that are able to capture this non-linearity. These growth models can be classified into two main groups, namely parametric and non-parametric models (Hauspie et al., 2004). Common parametric (or structural) models used include the Jenss-Bayley model, the Count model, Berkey-Reed 1st and 2nd order models, the Infant-Childhood-Puberty (ICP) model, the Preece-Baines model and the Gompertz, and common non-parametric (or non-structural) models are polynomials and splines (Olusanya and Renner, 2011, Gasser and Molinari, 2004, Goldstein and Pan, 1998, Hauspie et al., 2004). The parameters in the structural models represent particular growth milestones and have biological interpretation. For example, the ICP model summarises human growth into 3 overlapping components. The first two components which are predominantly controlled by growth hormones are the infancy component (from birth to around 3 years) and the childhood component (from 1 year to around 11 years). Apart from the linear and non-linear structural models mentioned above, researchers have used other non-structural models such as polynomials and splines to describe and monitor child growth (Olusanya and Renner, 2011, Botton et al., 2008). Despite their simplicity in fitting and in summarising the growth profiles, non-structural models tend to be unstable at the extremities, leading to imprecisions in

estimating early measurements. They also do not specifically define any particular form of the growth process and, as such, their parameters do not have any biological interpretation. (Hauspie et al., 2004, Singer and Willett, 2003). However they do provide summaries that can be used to examine relationships between life exposures and later health outcomes in a similar way parameters of structural models are used. If modelling over a wide time period, selection of meaningful knots for splines can be problematic, especially if there are limited number of data points, as this can lead to few individuals having measurements between knot points (Howe et al., 2013) .

Other studies that have looked at child growth have mostly tended to use growth centiles (Johnson et al., 2012b, Kalanda et al., 2005a, Maleta et al., 2003a, Mushtaq et al., 2012). Models used (structural, non-structural) depend on the purpose of the study. For example, studies that have used centiles have mainly been interested in monitoring growth in order to detect timing of growth faltering due to malnutrition by comparing child growth in their respective populations of interest to set growth standards. For instance, Maleta and colleagues (Maleta et al., 2003a), examined the timing of growth faltering in infants from Lungwena area, a predominately malnourished population in a rural area in Malawi. The growth centiles of the children were compared to the CDC and WHO reference chart. With centiles, data are analysed cross-sectionally in the computation of the mean and standard deviations at each age group. Johnson and colleagues (Johnson et al., 2012b), also used centiles to assess the relative risk of stunting, wasting and underweight in a cohort of children from the Infant Feeding Study in Andhra Pradesh, India. The growth of the children in the cohort was then compared to the WHO and NCHS reference charts. Unlike in the study by Maleta et al. (2003), Johnson looked at cross-sectional and longitudinal trajectories of growth. Figure 2.1 below shows the WHO

growth standard charts for boys and girls from birth to 5 years which would be used as reference in comparison of growth of children if growth centiles are used in modelling growth.

The best model to describe and represent the growth process, both at individual and population level, depends on the dimensions being measured e.g. weight, height, skinfold or circumferences. Apart from the dimensions, the fit of the model also depends on the frequency at which the measurements are taken e.g. weekly, monthly, yearly, and the period of growth that is being investigated e.g. infancy, childhood or adolescence (Hauspie et al., 2004, Karlberg, 1987). There are several growth models that have been found to fit well to the infancy or childhood period. These include the Jenss-Bayley, the Berkey-Reed and the Count models (Hauspie et al., 2004). The main common characteristic of these models is the presence of functions that capture the acceleration and deceleration in growth that occurs during this period of growth.



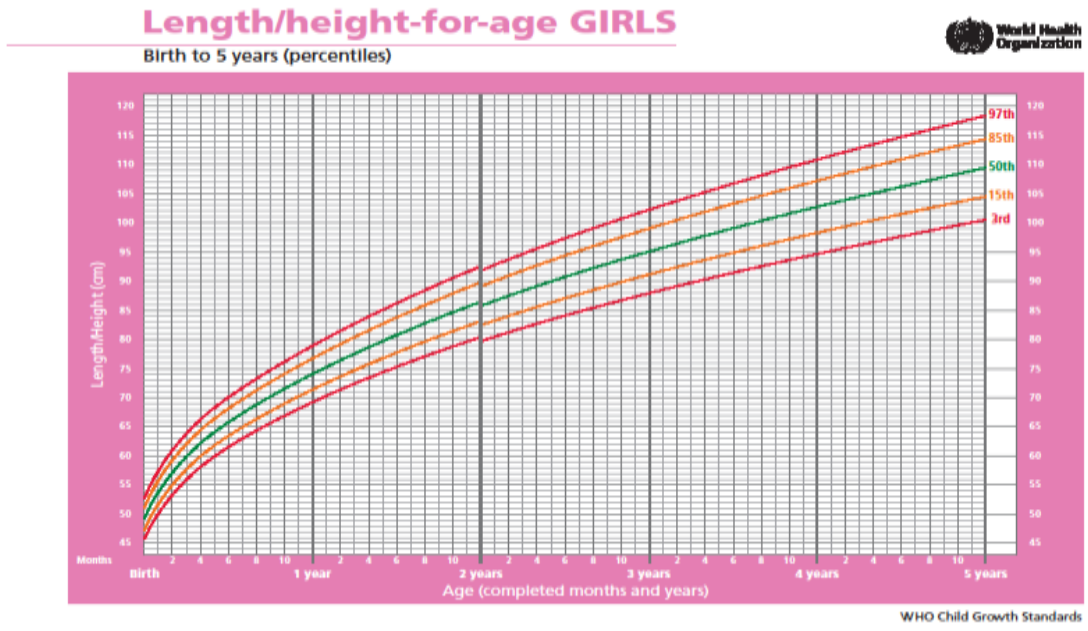
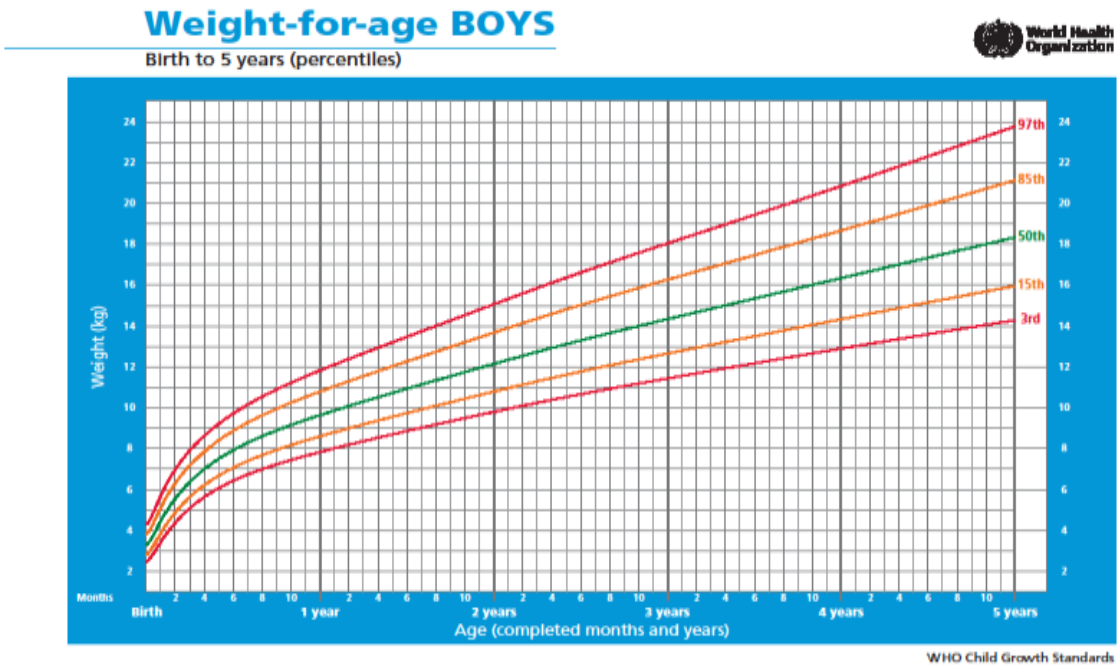


Figure 2.1 WHO growth percentiles for girls from birth to 5 years.

Source: www.who.int/childgrowth/standards/



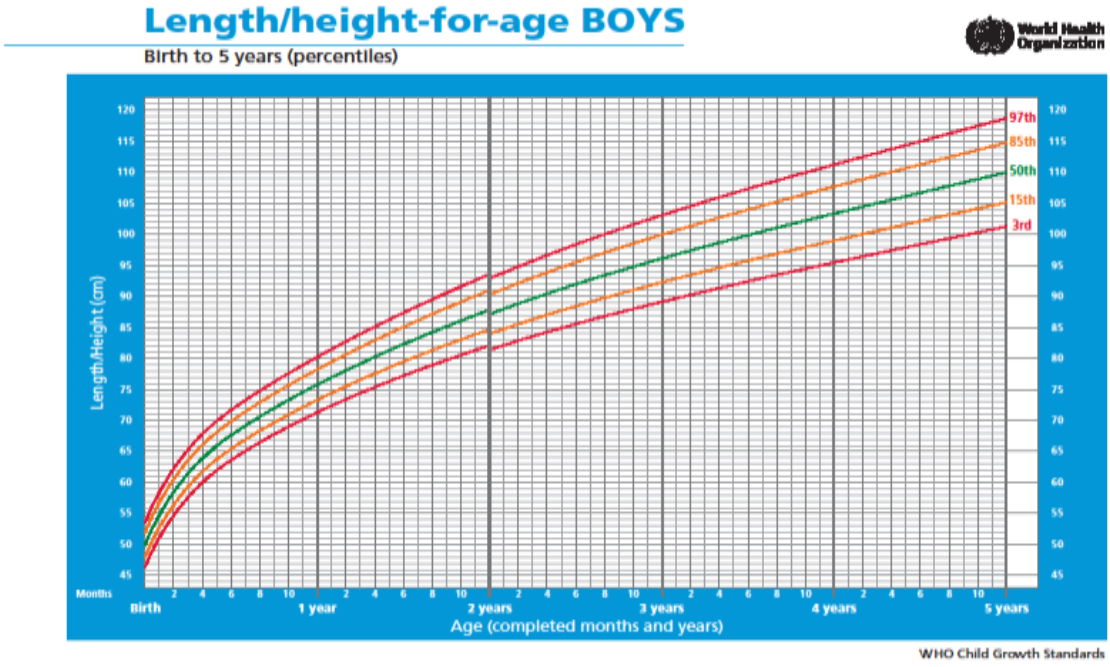


Figure 2.2 WHO growth percentiles for boys from birth to 5 years.

Source: www.who.int/childgrowth/standards/

2.2 STATISTICAL METHODS OF MODELLING PHYSICAL GROWTH

One of the challenges in the analysis of longitudinal studies is the correlated nature of the measurements. Traditional regression techniques such as Generalised Linear Models (GLM) are based on the independence of observation units assumption (Goldstein et al., 2002). In longitudinal studies, measurements on variables of interest are taken repeatedly over time, and these repeated measurements do not conform to the independence assumption as measurements taken closely together in time on the same individual are highly correlated. Thus, use of statistical methods that assume independence to understand biological phenomena, such as animal growth (which involves repeated measurements of growth variables) may lead to over-estimation of measures of effects. In contrast, mixed effects (or multi-level) models allow for effects at different levels to be estimated taking into account inter-relationships. Furthermore, while GLMs such as MANOVA require that there should be the same number of measurements for each individual and assume that these measurements are taken at the same time points, mixed-effects models do not have these restrictions. Individuals do not need to have the same number of measurements and since time is modelled as a continuous function, these measurements do not need to be taken at equal intervals (Cillessen and Borch, 2006, Goldstein et al., 2002). This flexibility allows mixed effects models to be used even when there are some missing measurements. However, there is still some loss of information due to the missing measurements and this can affect the precision of the estimates (standard errors of the estimates), since the overall sample size is reduced due to the missing measurements.

Apart from the clustering (hierarchy) of factors that affect human growth, another challenge in modelling growth in general is the autocorrelation of the growth measurement outcomes. Parametric models used to describe individual growth or to compare growth in different

populations are affected by the autocorrelation amongst measurements as well as the measurement intervals. Successive measurements will tend to be on the same side of the curve, producing residuals that are correlated (Bock and Du Toit 2003). Bock et al (Bock and Du Toit 2003) indicates that even for a well-fitting model, there might be some bias towards time points that are close together, if correlation is ignored (Bock and Du Toit 2003).

2.3 MISSING DATA IN LONGITUDINAL GROWTH MONITORING STUDIES

One of the main challenges in the analysis of longitudinal studies is the inevitability of missing data. Main reasons for missing data in such studies include death, migration, missed visits and reluctance by study participants to continue taking part in the study. Not being able to collect information from study participants lead to missing follow-up data and ignoring such participants in the analysis can lead to biased results, especially if participants with missing data have characteristics associated with the study outcome.

The risk of getting biased results in studies that have missing data depends on the reasons why the data are missing and can be commonly classified into 3 types (Little and Rubin, 2002). Missing values of a variable are classified as missing completely at random (MCAR) if the chance that the value is missing is not related to other observed or unobserved variables, and are classified as missing at random (MAR) if the chance that the value is missing is related to other observed (auxiliary) variables such sex and other demographic characteristics, but is not related to values that would have been observed in that particular variable (unobserved values). Missing values of a variable are missing not at random (MNAR) if the probability of a value missing is related to unobserved variables and also to the unknown values of that particular

variable (Peters et al., 2012, Spratt et al., 2010, Sterne et al., 2009). The overall effect size of ignoring missing data in the analysis will depend on the mechanism behind the missing data. Under MCAR, ignoring cases with missing data can still produce valid results. The major concern would be the reduced sample size which might in turn affect the precision of the estimates. Under MNAR, ignoring cases with missing data would lead to biased estimates and thus affect the validity of the findings (Blankers et al., 2010, Twisk and de Vente, 2002, Nakai and Ke, 2011).

2.4 OVERVIEW OF STATISTICAL METHODS OF DEALING WITH MISSING DATA IN LONGITUDINAL STUDIES

Different statistical methods for analysing longitudinal data are based on different missing data mechanism assumptions. Thus, it is important to understand the underlying missing data mechanism so that an appropriate statistical method is used. Methods such as Multivariate Analysis of variance (MANOVA) and Generalised Estimating Equations (GEE) are based on the MCAR assumption, while Mixed effects models (Random Coefficient analysis), and Weighted Generalised Estimating Equations are based on the assumption that data are missing at random (MAR) (Kwok et al., 2008, Touloumi et al., 2001, Twisk and de Vente, 2002). Statistical methods that have been recommended when data is missing not at random include Shared Parameter (joint) methods and Pattern-mixture models (Chang et al., 2009, Daniels and Hogan, 2008, Gad and Ahmed, 2007).

Another aspect that has to be considered in choice or comparison of statistical methods for longitudinal data is the type of outcome variable (Chirwa et al., 2009, Twisk, 2004). Twisk et

al found that using GEE on a dichotomous outcome variable produced different parameter and standard error estimates when used on an incomplete dataset compared to a complete one (Twisk, 2004). Comparison of GEE and random coefficient analysis also produced different results when applied to a dichotomous outcome but similar results when applied to a continuous outcome.

2.4.1 Imputation methods

Over the years, researchers have used different methods to impute for missing data in longitudinal studies. Statistical methods that can be used to impute for the missing data will increase the amount of information available to make inferences about the study population. This leads to increased statistical power and reduced standard errors of parameter estimates (increased precision) (Demirtas, 2010, Diggle et al., 1994, Engels and Diehr, 2003). Imputation involves calculation of values to replace those missing, and the different imputation methods can broadly be classified into cross-sectional and longitudinal methods. The cross-sectional methods use population group information to impute for missing values, while longitudinal methods use the longitudinal nature of the data in each case to impute values. Table 3.1 gives a summary of some of the imputation methods that have been used to deal with missing data in longitudinal studies.

These imputation methods are based on different assumptions about the underlying missing data mechanism (Engels and Diehr, 2003, Twisk and de Vente, 2002, Yang et al., 2008). Apart from missing data mechanisms, which imputation method used also depends on the type of

variables under consideration. For example, linear regression methods which is one of the cross-sectional methods is not recommended for imputing for missing data in an outcome variable if there is missing data in the predictor variables, since the method imputes for missing data in the outcome variable at a particular time point using information from predictors at that given time point (Twisk and de Vente, 2002). Thus, if predictors have missing data, there would be limited information that can be used to predict the missing values. Studies have shown that in general, methods that use the longitudinal nature of the data to impute values to be better than the cross-sectional population based methods (Engels and Diehr, 2003, Grittner et al., 2011, Twisk, 2004).

One of the most widely used methods of imputing data that uses the longitudinal nature of the data is the Last Observation Carried Forward (LOCF). The method replaces the missing value with the last observed value in the same subject. While this method might be easy to use and appropriate in some circumstances, it would be inappropriate to use in modelling human physical growth measurement, since physical growth measurements changes with time especially in early childhood.

One of the common longitudinal imputation methods that have been used in growth measurements is linear interpolation (Tang et al., 2005, Twisk and de Vente, 2002) . However, like the LOCF, the assumption of linear change in the growth measurements might not be appropriate especially in infancy and early childhood, where it is known that children undergo rapid growth followed by some deceleration. Linear interpolation is likely to be affected by the distance between available data points and the period of growth, that is whether one is looking at early childhood (where growth is rapid) or late childhood (where a child experiences deceleration in growth).

With advances in statistical software, multiple imputations which can be considered as an improvement to cross-sectional or longitudinal methods, has become one of the commonest methods used in dealing with bias and loss of information. Multiple Imputation involves the use of any of these methods. However, in multiple imputation, for each missing value a set of values are calculated (multiple values) based on assumptions about the relationship between the outcome variables, the predictors and other covariates. For example, if it is assumed that there is a linear relationship between an outcome variable and the predictors, multiple values would be calculated for each missing value using linear regression creating multiple datasets and summary statistics (regression parameters) would then be combined into one summary statistics. Because multiple imputation allows for the uncertainty about the missing data by creating a number of datasets in which all missing values are replaced by the imputed values, there is generally an improvement in the imputed value estimate. However, multiple imputation can be complex especially where there are a large number of variables with large numbers of missing data. It can also produce parameter coefficients with larger standard errors than those from a complete dataset, due to the high variability in the variable produced by estimation of the missing values. For physical growth measurements, large standard errors would mean less precision in the estimation of the model parameters.

Like mixed effects regression models, the multiple imputations are based on the assumption that data are MAR. While MI can help in reducing bias, Kenward and Carpenter (2007) caution against its indiscriminate use (Kenward and Carpenter, 2007). They argue that MI can bring in some bias if the imputation model is wrongly defined. Under MAR, the probability of missing values is related to some observed variables. Thus it is important to identify any factors associated with the outcome and to include such factors in the imputation model (He, 2010, Kenward and Carpenter, 2007, Sterne et al., 2009).

The main challenge in deciding which imputation method is better when using real life dataset is on setting appropriate assumptions regards the underlying missing data mechanism. Imputation methods assume particular missing data mechanism, which in the absence of the true value (since the true values for the missing data are unknown) can only be speculated (Engels and Diehr, 2003, Twisk and de Vente, 2002, Yang et al., 2008). In their simulation studies, Engels et al. create missing data from a complete data set to compare the imputation methods (i.e. true values for the missing data are known) and also assumed that the missing data mechanism was random. In real life, the true values will not be known and the missing data mechanism has to be investigated. These two aspects pose the major challenge in deciding which imputation method to use, and can lead to one imputation method giving better results in one variable or situation (e.g. when the amount of missing data varies) and worse results in another variable or situation.

2.4.2 Available Case Analysis methods

Advances in statistical methods have also seen researchers use the available information in a data set to measure effects rather than excluding cases where any data are missing. The Available Case Analysis (ACA) methods include Linear Mixed Effects (LME) regression and Generalised Estimating Equations (GEE). The advantage of using LME over GEE in modelling physical growth is that LME allows for modelling of random effects and can therefore take account of the individual variation in growth amongst subjects (Peters et al., 2012, Twisk and de Vente, 2002). The superiority of ACA methods over CCA is due to the fact that ACA methods incorporate the partial information from cases with missing data. However, ACA methods can also lead to biased results if missing data are not MCAR.

Several studies have evaluated the impact of ignoring missing data on precision of model parameter estimates (Blankers et al., 2010, Molenberghs et al., 2004, Twisk and de Vente, 2002). For example, Twisk et al. (Twisk and de Vente, 2002), found significant differences in regression coefficients of a predictor derived using MANOVA for repeated measures (which ignores subjects with missing data) and those derived using GEE analysis (which uses available information from those with missing data). Blankers et al. (Blankers et al., 2010) also compared the performance of several methods of handling missing data for both normally distributed and non-normal data. The study found that Multiple Imputation produced the most valid parameter estimates while complete case analysis (ignoring those with missing data) produced less valid results. When applied to non-normally distributed data, multiple imputation still produced optimal results. Peters et al. compared the use of MI and Linear mixed effects on missing repeated outcome measurements (Peters et al., 2012). The study found that performing multiple imputations before using linear mixed models had no added value. In other words, it was found that use of linear mixed effect modelling in handling missing data in repeated outcome measures was sufficient.

Table 2.1 Imputation methods used in handling missing data in longitudinal studies

Class	Method	Description	Pros	Cons
Cross-sectional	Mean of series	Missing value substituted by the average value of the available data for that variable at each particular time.	• Conceptually straight forward. • Minimal computations.	• All missing values at time t will be replaced by same value. This leads to reduced variance in the imputed data. • Does not take into account temporal patterns in data
	Hot-decking	Random selection from those observed who have comparable cases	• Conceptually straight forward. • Minimal computations.	• Can lead to reduced variability. • Difficulty in finding similar cases.
	Cross-sectional linear regression	Missing value is substituted by the predicted value from the regression of outcome Y on all available predictor variables.	• Conceptually straight forward. • Minimal computations.	• Participants with same covariates will have identical imputed values, leading to reduced variance in the imputed data. This leads to inappropriate standard errors and falsely narrow confidence intervals. • Can only be used if the outcome is missing and not the predictors
Longitudinal	Last Observation Carried forward (LOCF)	Missing value at time t is replaced by value observed at time t-1.	• Conceptually straight forward. • Minimal computations. • Used for both continuous and categorical variables.	• Assumes variable is more or less constant over time. • Does not take into account the length of the time interval between data points.
	Linear Interpolation	Missing value at time t is imputed by the average of the value at t-1 and t+1	• Uses the individual's data to impute for the missing value.	• Assumes change over time is linear. • Assumes non-monotonic missing data patterns

Table 2.1 Continued				
Class	**Method**	**Description**	**Pros**	**Cons**
Longitudinal	Individual regression imputation	Missing value is substituted by the predicted value from the regression of outcome Y and time at which value is missing.	• Uses the individual's data to impute for the missing value.	• Does not take into account the uncertainty of the imputation process.
	Population regression	Missing value is substituted by predicted value from the regression of outcome Y on previous measurements of Y, other predictors and time when value is missing.	• Uses the individual's data to impute for the missing value.	• Depends on how good the relationship is between the outcome and the predictors used. • Can only be used if predictors have no missing data. • Conceptually complex.
	Multiple Imputation	Involves several imputations for each missing value, creating multiple datasets and the analysed to derive required summary statistics and uses other method outlined above to derive imputed values.	• Adjusts for the uncertainty of the imputation process by combining within-imputation and between imputation variances. • Flexible	• Conceptually complex. • Require more computational power. • Performance depends of how good the imputation model is.

Source: (Blankers et al., 2010, Engels and Diehr, 2003, Grittner et al., 2011, Spratt et al., 2010, Sterne et al., 2009, Tang et al., 2005, Twisk, 2004, Twisk and de Vente, 2002)

2.5 KEY POINTS FROM LITERATURE REVIEW

In summary as outlined above, studies have modelled different periods of human growth using different types of growth curves (structural models, non-structural models and centiles). However, none have compared the fit of these models to growth data from an African setting. As it has been outlined, human growth process is affected by several factors including genetics and nutrition. Studies that have compared different growth curves have used data from different genetical and environmental settings and/or different periods of childhood (Grimm et al., 2011, Johnson et al., 2013, Simondon et al., 1992). Apart from limited application in African settings, no study has compared the performance of the different growth curves under varying number of data points (frequency of measurements) and examined the performance of the curves in the presence of missing data. Despite there being a substantial body of knowledge regards methods of dealing with missing data in longitudinal studies, there is limited knowledge on longitudinal outcomes that follow a particular mathematical function or trend in measurements. Early childhood growth measurements in general follow particular trajectories and taking account of such in dealing with missing data cannot be overemphasised. In addition, none of the studies that have compared different methods of dealing with missing data in longitudinal studies have looked at the effects of time intervals between data points on the performance of the different methods.

In summary, when analysing longitudinal growth data, it is important to consider all the different issues outlined above in the selection of the growth models, imputation or statistical methods to be used. It is also important to acknowledge the limitations of the chosen methods.

PART 2: METHODS

Part 2 of the thesis consists of only one chapter. Chapter 3 describes the sources of the data used in the application of the statistical methodologies as well as the actual methodologies used in order to answer the statistical and empirical research objectives of the PhD study.

CHAPTER 3: METHODS AND DATA

This chapter gives a brief description of the 2 birth cohorts used in the thesis and the data used. It further describes the statistical methodologies used to answer the thesis' 3 broad statistical and empirical research objectives.

3.1 STUDY AREAS AND PARTICIPANTS.

Data for this PhD study were taken from the Lungwena Child Survival Study from Malawi and the Bone Health study, a sub-cohort of the Birth to Twenty (BT20) cohort study from Johannesburg, South Africa.

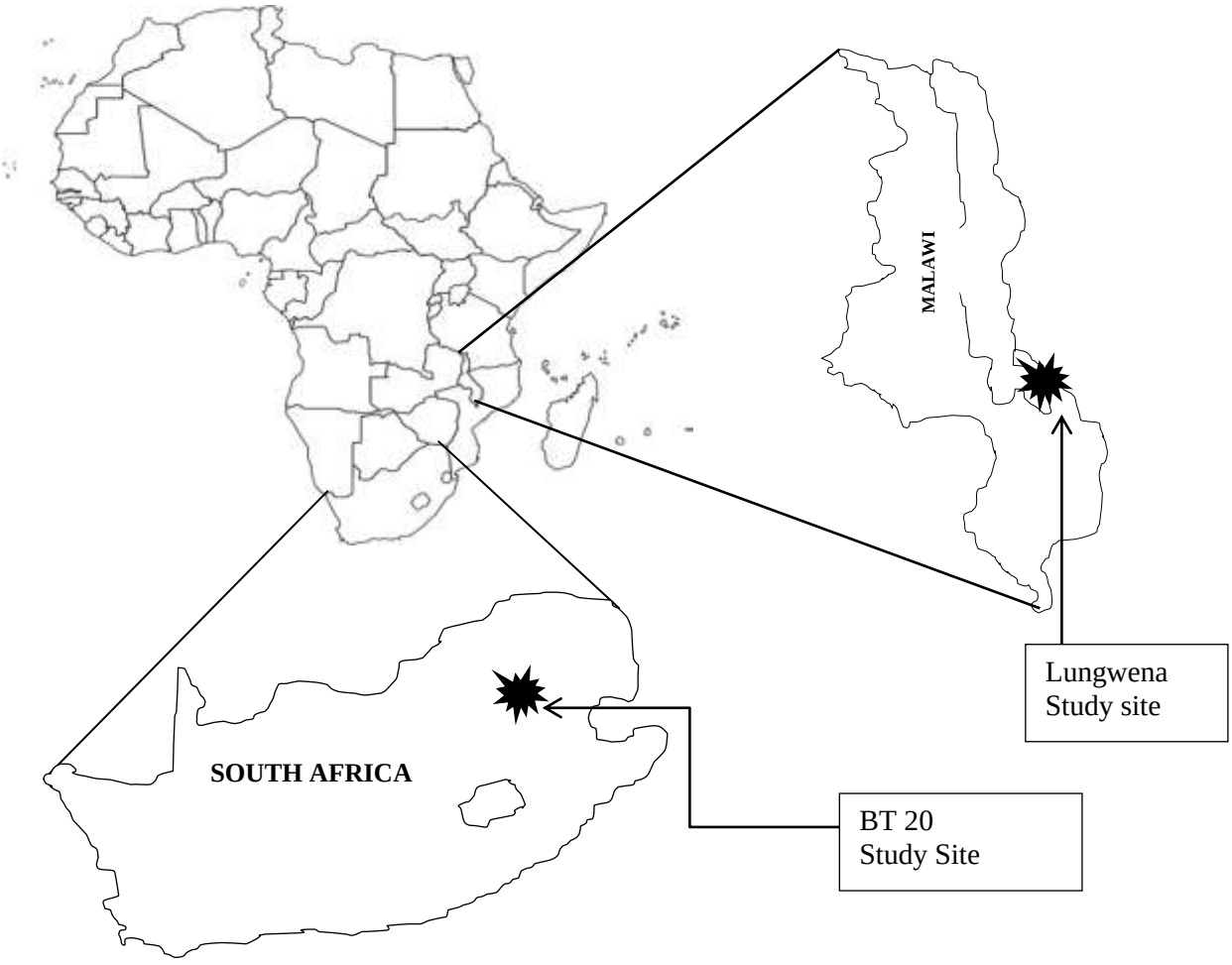


Figure 3.1 Maps showing the location of the 2 cohorts

Source: www.imgarcade.com & www.hdimagelib.com

3.1.1 Lungwena:- Malawi

The Lungwena Child Survival Study (LCSS) is an on-going population-based cohort study of maternal and child health and is set in Mangochi, a rural district in southern Malawi. Lungwena is a 100 km rural area located at the south-eastern shore of Lake Malawi in Southern Malawi, Mangochi District. The study area is the catchment area of a public health centre. According to the most recent census in the area (NUFU 2004), Lungwena has a total of 23058 inhabitants living in 5174 households. These households are spread across 26 villages over the area, and the villages vary in size between 40 and 503 households. The average size of a village is about 200 households. The average household has 4.5 members. Three-quarters of all households are headed by males, while one-quarter are headed by females. Farming and fishing are the two main income sources for households in Lungwena, with 60 % of the male population working as farmers and about 24% working as fishermen. Education levels among both men and women are low, with 64 % of men and 80% women having no formal education.

The LCSS cohort comprised of live-born singleton offspring of a cohort of 795 women who attended an antenatal clinic at Lungwena Health Centre between June 1995 and September 1996. Mothers were recruited in mid pregnancy at first booking of antenatal care at the health centre. Background data and maternal health characteristics were collected at enrolment and during follow up. Their live-born offspring were then intensively followed up from birth. Due to high enrolment rates, the study cohort consisted of approximately 95 % of all new born children in the area (Espo et al., 2002). Delivery events were recorded during home visits as soon as possible after birth, and the study physician examined all the infants at the health centre within a month of delivery. Monthly visits were then done by research team during the first year of life. At 12 months, about 23 % of the children had either died or were lost to

follow up. At 36 months, this loss had increased to about 25% (Maleta et al., 2003a). By the time the cohort was about 4 years; a third of the children had either died or been lost to follow up.

Apart from information on feeding patterns and other health measures, anthropometric data were collected every month from birth of each child until the child was about 18 months. The data collection was increased to every 3 months until the child was about 60 months. Measurements were then taken at 6 years of age, 8-9 years, 10 years, 12 years and 15 years of age (Espo et al., 2002, Maleta et al., 2003a, Maleta et al., 2003b).

3.1.2 Soweto (Johannesburg):- South Africa

Soweto is an urban area of the City of Johannesburg in Gauteng, South Africa. It borders the city's mining belt in the south. Birth to Twenty (BT20) is Africa's largest and longest running study that is looking at child and adolescent health and development, and also one of the few large-scale longitudinal studies in the world. BT20 started in 1989 as a longitudinal birth cohort study of children's health and development, during a period of rapid social and political change in South Africa, and began to track the development of 3,273 newborn singleton infants who were recruited in a 7 week period. Other criteria for entry into the study were that both the mother and baby were supposed to remain in the area until the child was 6 months old (Richter et al., 1995).

The period of the study had overlapped with sweeping demographic and health transitions. The first round of the study began in 1989/1990, and collected information from still-pregnant

mothers on their general demographic characteristics, and conditions of the pregnancy. Further round of assessments and surveys were done at three and six months. After that, data was obtained on an annual basis. The questions in the yearly surveys cover a wide range of topics that looked at both the physical health and cognitive development of the child, his or her environment, education level, nutrition status, as well as socioeconomic class. By the age of 16 years, more than 70% of the original cohort of the children and their families in Soweto-Johannesburg were still being followed up (Richter et al., 2007).

The Bone Health (BH) study was constituted as a sub-cohort of BT20 when the children were 9 years of age with the aim of investigating in more detail factors that influence bone mass accretion during puberty and adolescence. A supplementary sample of 120 white children born during the same period as the original BT20 cohort was recruited at the age of 10 years to increase the white sample size. Despite these supplementary 120 white children being born in different areas from the BT20 cohort, there were no significant differences in their birth weight, maternal age and education, and socioeconomic status between the supplementary children and the original white participants of the cohort. This PhD study has only used data from black participants of the BH study.

3.2 ETHICAL REQUIREMENTS

Both studies sought ethics approval from relevant committees. Ethics approval for the BT20 study was given by the University of the Witwatersrand's Human Research Ethics Committee. The Lungwena Child Survival Study sought approval from the Malawi National Health Sciences Research Committee. In both studies, informed consent was sought from study participants.

For this particular PhD study, separate ethics approvals were sought from the University of the Witwatersrand's Human Research Ethics Committee as well as from the University of Malawi, College of Medicine's Research and Ethics Committee (See Appendix A). No re-consenting was sought from participants since the PhD study used historical data that had already been collected for the initial research questions in each respective study.

3.3 METHODOLOGY AND DATA ANALYSIS

This section outlines the methodologies used in the selection of analysis samples for the 3 components of the thesis and the statistical methods used in the analysis of data for each of the 3 components. The 3 components of the PhD study are:

i) Comparison of growth models

ii) Methods of dealing with missing weight and height measurements

iii) Comparison of child growth in African settings and examination of relationship between postnatal growth and early adolescent obesity.

Thus, the first sub-section is looking at the methodology used in the comparison of growth models analysis. The second sub-section is looking at the methodology used in dealing with missing data, while the third sub-section is looking at methodology used in examining the relationship between postnatal growth and early adolescent obesity.

3.3.1 Comparison of growth models

This sub-section outlines the inclusion criteria for the sample used in the comparison of growth model analysis of the study and the statistical methods used in the modelling.

3.3.1.1 Subjects and methods

This component of the study used weight and height measurements from participants of the Bone-Health (BH) study and Lungwena Child Survival Study (LCSS) as primary outcomes. The following exclusion criteria were used:

- Gestational age < 37 weeks.
- All participants with weight-for age z-scores (WAZ) or with height-for-age z-scores (HAZ) that were consistently (on at least 3 occasions) greater than +2 or less than -2.
- Participants with less than 5 weight or height measurements.

The exclusion of children with WAZ/HAZ scores greater than +2 or less than -2 was done to make only children exhibiting normal growth trajectories were used in the modelling process since the growth models being used were defined for children following normal growth trajectories. The exclusion of participants with less than 5 weight or height measurements was done to make sure that there were sufficient measurements to fit the Adapted Jenns-Bayley model (which had the largest number of parameters. Due to the absence of birth length in the BH study and to meet the inclusion criterion of a minimum of 5 data points per individual child, 2 analysis datasets were derived from the BH cohort. The dataset for height started at 1 year while the dataset for weight measurements started at birth.

Before fitting the growth curve, descriptive statistics such as means, standard deviations, and frequencies were calculated. T-tests were used to compare mean weights and heights at each measurement occasion. These comparisons were done on both the overall data set and the final 'analysis data set'. The analysis dataset refers to the dataset derived after removing participants that met the exclusion criteria outlined above. Proportions of males, small for gestation age (SGAs) and firstborns in the overall data set were also compared to those in the final 'analysis

data set' to see whether there were any differences in characteristics between the two datasets. The datasets were then converted to long form in order to fit the mixed effects models. Several growth models were fitted to the data using a mixed effects modelling approach (Singer and Willett, 2003, Steele, 2008).

3.3.1.2 Growth Models

The following structural (parametric) and non-structural (non-parametric) models were used.

1) The Berkey-Reeds 1st order (Reed1) model which is defined as:

$$y_i = \beta_0 + \beta_1 t_i + \beta_2 \ln(t_i) + \beta_3 \frac{1}{t_i} \qquad i = 1,2....n \qquad \textbf{(1)}$$

2) The Count model:

$$y_i = \beta_0 + \beta_1 t_i + \beta_2 \ln(t_i + 1) \qquad i = 1,2....n \qquad \textbf{(2)}$$

3) The Jenss-Bayley model:

$$y_i = \beta_0 + \beta_1 t_i - \exp(\beta_2 + \beta_3 t_i) \qquad i = 1,2....n \qquad \textbf{(3)}$$

4) The adapted Jenss-Bayley model

$$y_i = \beta_0 + \beta_1 t_i + \beta_2 t_i^2 - \exp(\beta_3 + \beta_4 t_i) \qquad i = 1,2....n \qquad \textbf{(4)}$$

5) The 2nd Order Polynomial:

$$y_i = \beta_0 + \beta_1 t_i + \beta_2 t_i^2 \qquad i = 1,2....n \qquad \textbf{(5)}$$

6) The 3rd Order Polynomial:

$$y_i = \beta_0 + \beta_1 t_i + \beta_2 t_i^2 + \beta_3 t_i^3 \qquad i = 1,2....n \qquad \textbf{(6)}$$

where y_i represents weight/ height of child at measurement occasion ***i*** and t_i represents age of the child at measurement occasion ***i.***

For the Reed1 model, y_i represents weight/ height of child at measurement occasion ***i*** and t_i represents age of the child at measurement occasion ***i,*** the function parameter β_0 is related to the baseline weight or height at birth, β_1 is related to the linear component of the growth velocity, β_2 is related to the deceleration in growth velocity and β_3 represents an inflection point that allows growth velocity to peak after birth rather than at birth.

For the Count model, the function parameter β_0 is related to the baseline weight or height at birth, β_1 is related to the linear component of the growth velocity, and β_2 is related to the deceleration in growth velocity. Similarly for the Jenss-Bayley and the adapted Jenss-Bayley model, the function parameter β_0 is related to the baseline weight or height at birth, β_1 is related to the linear component of the growth velocity, while $\exp(\beta_2 + \beta_3 t_i)$ and β_2 represents the decrease in growth velocity shortly after birth respectively, and $\exp(\beta_3 + \beta_4 t_i)$ represents the inflection point.

3.3.1.3 Mixed Effects Modelling

The models above were fitted to weight and height measurements using linear mixed effects (LME) modelling under the general framework of General Linear Models (GLM). The general structure of the LME is given by

$$\mathbf{y} = \boldsymbol{X\beta} + \boldsymbol{Zu} + \boldsymbol{\varepsilon} \qquad \textbf{(7)}$$

where

y is the ***n x 1*** vector of the observed weight/height

X is a ***n x p*** matrix of the fixed effects representing the different growth models,

β is a **p *x* 1** vector of the coefficients,

and **Z** is a ***n x q*** matrix of the random effects **u**.

the ***n x 1*** vector of errors, is assumed to be multivariate normal with mean zero and variance of matrix $\sigma_{\varepsilon}^{2} I_{n}$.

For each growth model, the following 2 general model structures were defined from model (7) to test for the significance of the sex and age-sex interaction in the fixed effects.

$$y_{(k)ij} = f_{(k)}(t_{ij}) + \beta_1 Sex + \varepsilon_{ij} \quad \textbf{(8)}$$

$$y_{(k)ij} = f_{(k)}(t_{ij}) + \beta_1 Sex + \beta_2 Sex * t_{ij} + \varepsilon_{ij} \quad \textbf{(9)}$$

where

$t_{ij} \geq 0$ and represents the age of child ***i*** at measurement occasion ***j***

y_{ij} represents weight or height of child ***i*** at measurement occasion ***j***.

ε_{ij} are random residuals

$f_{(k)}(t_{ij})$ represents fixed effects

Sex= 0 if boy. Sex=1 if girl.

Models 8 and 9 are both fixed effects models and were compared using the likelihood ratio test. Random components were systematically added to the fixed effects to create a mixed effect models with general structure as defined in equation 10.

$$y_{(k)ij} = f_{(k)}(t_{ij}) + \beta_1 Sex + \beta_2 Sex * t_{ij} + h_{(k)}(t_{ij}) + \varepsilon_{ij} \quad \textbf{(10)}$$

where $h_{(k)}(t_{ij})$ represents random effects

For each growth curve, the following levels of random effects were fitted:

Model with random intercept only:- $h_{(k)}(t_{ij}) = u_0$ **(11)**

Model with random intercept and slope:- $h_{(k)}(t_{ij}) = u_0 + u_1 t_{ij}$ **(12)**

Equations 13-18 represent multilevel model structures with random intercept and slope for equations 1-6.

The Berkey-Reeds 1st order (Reed1) model which is defined as:

$$y_{ij} = \beta_0 + u_{0j} + (\beta_1 + u_{1j})t_{ij} + \beta_2 \ln(t_{ij}) + \beta_3 \frac{1}{t_{ij}} + \varepsilon_{ij} \quad \textbf{(13)}$$

The Count model:

$$y_{ij} = \beta_0 + u_{0j} + (\beta_1 + u_{1j})t_{ij} + \beta_2 \ln(t_{ij} + 1) + \varepsilon_{ij} \quad \textbf{(14)}$$

The Jenss-Bayley model:

$$y_{ij} = \beta_0 + u_{0j} + (\beta_1 + u_{1j})t_{ij} - \exp(\beta_2 + \beta_3 t_{ij}) + \varepsilon_{ij} \quad \textbf{(15)}$$

The adapted Jenss-Bayley model

$$y_{ij} = \beta_0 + u_{0j} + (\beta_1 + u_{1j})t_{ij} + \beta_2 t_{ij}^2 - \exp(\beta_3 + \beta_4 t_{ij}) + \varepsilon_{ij} \quad \textbf{(16)}$$

The 2nd Order Polynomial:

$$y_{ij} = \beta_0 + u_{0j} + (\beta_1 + u_{1j})t_{ij} + \beta_2 t_{ij}^2 + \varepsilon_{ij} \quad \textbf{(17)}$$

The 3rd Order Polynomial:

$$y_{ij} = \beta_0 + u_{0j} + (\beta_1 + u_{1j})t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3 + \varepsilon_{ij} \quad \textbf{(18)}$$

where y_{ij} represents weight/ height of child *j* at measurement occasion ***i*** and t_{ij} represents age of the child *j* at measurement occasion ***i.***

Higher levels included systematic addition of higher order functions such as ln (t_{ij}), $(t_{ij})^2$ or 1/ (t_{ij}) to models (13-18). The LR test was then used to assess the significance of adding each random effects term, using significance level of 5%.

3.3.1.4 Random Effects

In the random component **Zu** + **ε** of the mixed effect model in equation (7), it is assumed that **u** has a variance-covariance matrix **G** and that $\text{var}\begin{bmatrix} u \\ \varepsilon \end{bmatrix} = \begin{bmatrix} G & 0 \\ 0 & R \end{bmatrix}\sigma^2$.

The random effects **u** is represented by variance components estimated together with the overall residual variance (σ^2). It was assumed that the covariance structure for **u** was unstructured, which assumes distinct variance and covariance estimates. For a mixed model with random intercept and slope, the unstructured **G** would be represented by

$$G = \text{var}\begin{bmatrix} u_{oi} \\ u_{1i} \end{bmatrix} = \begin{bmatrix} \sigma_0^2 & \sigma_{01} \\ \sigma_{01} & \sigma_1^2 \end{bmatrix}.$$

The 'unstructured' covariance structure is a more relaxed assumption than other structures such as 'independent', which would assume that the variation in the slope is independent of the intercept. This could clearly be a problematic assumption when modelling human growth. The covariance estimates in a mixed effects model of growth can be interpreted in terms of the relationship between initial size and subsequent growth rate. For example, a negative estimate in a model with a random slope and intercept would indicate that children with low initial size (weight/ height) are exhibiting faster growth.

The random residuals **ε** were assumed to have an independent structure, i.e. var (**ε**) = $\sigma_\varepsilon^2 I_n$.

3.3.2 Missing data in physical growth measurements

This sub-section outlines the inclusion criteria and methodology used in dealing with missing weight and height measurements in this study.

3.3.2.1 Subjects and Methods

The analysis of missing data in the 2 cohorts was done in 2 components. The first component used participants with complete weight and height measurements. For the BH study, which had data collection waves at birth, 3 months, 6 months, 1 year, 2 years, 4 years, 5 years, 7/8 years, 9 years and at 10 years, a complete case for weight model was defined as an individual with weight measurements at birth, 1 year, 2 years, 4 years, 5 years, 7/8years, 9 years and at 10 years. The removal of observations at 3 and 6 months were necessitated by the very high percentage of missing information at these 2 time points, which was 68% and 77% respectively. Including 3 months and 6 months would have drastically reduced the sample size for analysis. Table 3.1 shows a summary of the percentage of missing data in the 2 cohort. The exclusion of the 3 months and 6 months data collection waves reduced the total number of data points per individual from 10 to 8. For the height model, a complete case was defined as an individual with height measurements at all data points from 1 year to 10 years. This was due to the unavailability of birth length measurements and the high percentage of missing measurements at 3 and 6 months.

Table 3.1 Percentage of missing data at each data collection point.

Time point	BH cohort			Lungwena cohort		
	Overall % missing	% missing (Boys)	% missing (Girls)	Overall % missing	% missing (Boys)	% missing (Boys)
3m	22	22	21	67	67	80
6m	24	24	24	77	76	94
9m	21	21	21	…..	…..	…..
12m	20	20	21	24	25	28
15m	23	25	22	…..	…..	…..
18m	22	23	21	…..	…..	…..
21m	21	21	22	…..	…..	…..
24m	22	20	24	28	30	32
27m	22	21	23	…..	…..	…..
30m	24	26	22	…..	…..	…..
33m	22	21	24	…..	…..	…..
36m	23	22	23	…..	…..	…..
39m	23	24	23	…..	…..	…..
42m	23	23	23	…..	…..	…..
45m	24	23	24	…..	…..	…..
48	23	23	22	15	16	16
51	23	23	23	…..	…..	…..
54	22	21	23	…..	…..	…..
57	22	22	22	…..	…..	…..
60	23	23	23	20	17	28
72	24	24	24	…..	…..	…..
96	24	23	25	16	15	19
108	…..	…..	…..	24	22	32
120	24	23	24	17	15	23

(…..)= data point not available

Although the data collection waves for the Lungwena cohort were more intensive (monthly from birth to 18 months, 3-monthly from 18 months to 60 months and then at 6 years, 8-9 years, 10 years), we defined ‘complete case’ as an individual with data at all 3-monthly data collection waves up to 60 months as well as with data at all the data points greater than 60 months. This again was done to increase the sample size of participants who would meet the criteria for ‘complete case’. The total number of data points for the Lungwena cohort was thus reduced from 36 to 24. In both cohorts, all participants with gestation age of less than 37 weeks were also excluded from analysis.

In the second component of the analysis of missing data, the study used all participants with sufficient data points (i.e. minimum of 4 data points).This was the minimum number of data points required to fit a Berkey-Reed model used in the imputations and modelling process. Apart from the gestation age being >= 37 weeks, participants with 4 or more data points were included in the analysis.

3.3.2.2 Missing data simulation

For the first component, simulated missing data were created from the complete cases, while keeping the observed measurements as outlined in Figure 4. Patterns of missing data were first examined before assumptions of the mechanism behind missing data were made. Biologically, our interest was on how weight or height measurements of the children change over time. Statistically, we were interested in the regression of weight/height measurements on time. Without loss of generality, the following notations were used in exploring the missing data mechanism (MDM).

Y = outcome variable (weight/height measurements)

X= Covariate of direct interest (time of the data collection wave, which roughly represented age of the child, e.g. 3 months, 6 months, 1 year, etc.)

R= response indicator = 1 if ***Y*** was observed

0 if ***Y*** was not observed.

V= other auxiliary non-time-varying covariates (sex of child, maternal height).

The MDM is defined based on the association between Y and R. Using the above notation, the ***Y***'s are said to be missing at random (MAR) if $f(r|y,x) = f(r|x)$, and are considered as missing completely at random if $f(r|y)=f(r)$. If there exists at least one value of y such that $f(r|y) \neq f(r)$, then the missing values of ***Y*** are missing not at random (MNAR).

We examined the patterns in ***R*** at each data collection wave (***X***). Even though, there were a high proportion of missing values at 3 and 6 months in the BH cohort, we did not think the probability of missing values at each data collection wave (***X***) depended on the weight or height measurements. The high percentage of missing data at 3 and 6 months were due to logistical problems during the initial phases of the study rather than anything to do with the outcome measures themselves. Based on the results from the other time points, MAR was adopted. In other words, the missing data mechanism was a random deletion mechanism within distinct level of ***X*** (i.e. at each data collection time). Thus, missing data were simulated from the complete dataset by randomly deleting some weight or height measurements in order to achieve the same missingness pattern as in the original dataset. Datasets were created with the same percentage of missing values as the original dataset, which was around 20 %. To investigate reliability and coverage of the results, 50 bootstrap samples were drawn from the dataset with simulated missing data for weight and height measurements for each cohort, giving a total of 200 datasets.

The study methodology for the second component of the missing data analysis is outlined in Figure 3.2.

3.3.2.2.1 Imputation of missing height/ weight measurements

Three different methods were used in dealing with the missing weight and height measurements as shown in Figure 3.2. For Multiple Imputation (MI), 10 imputations for each missing value were done.

The strategy for MI was as follows:

i) Fit a parametric imputation model that characterized the observed-data distribution ***f (y|v, x, r=1)***. The Reed1 model (model 1), which is used to describe physical growth in childhood was used to characterize the observed data distribution. The model had previously been found to fit to the 2 cohorts better than other available growth models.

ii) For missing weight/height measurements, age of child at time point X, and other covariates(V) were used in the imputation of Y^*s.

iii) The missing Y's were replaced by Y^*s, creating 10 datasets.

iv) The Reed1 model was then fitted to the 10 datasets.

v) The overall model parameter estimates and their standard errors were then derived from the models fitted to the 10 datasets, where the overall model parameter estimate is given by the sample mean:

$\hat{\theta} = (1/10)\sum_{j=1}^{10} \hat{\theta}_{(j)}$, where $\hat{\theta}$ represents an estimate of each parameter of the Reed1 model.

And the estimate of variance of $\hat{\theta}$ combines the between dataset and within dataset imputation variance and is given by:

$$\text{Var}(\hat{\theta}) = \frac{1}{9}\sum_{j=1}^{10}(\hat{\theta}_{(j)} - \hat{\theta})^2 + \frac{1}{10}\sum_{j=1}^{10}\text{var}(\hat{\theta}_{(j)}) \quad \text{where} \quad \text{var}(\hat{\theta}_{(j)}) = \left\{s.e(\hat{\theta}_{(j)})\right\}^2$$

The strategy behind the regression imputation was as follows:

i) Fit imputation model that characterized the observed data (same model as in MI above).

ii) For missing values, plug in (***X, V***) to get a predicted (imputed) value ***Y***.

iii) Replace missing ***Y***'s with $\boldsymbol{Y}^*$s.

iv) Fit growth model as if we had full data.

Apart from being used as the imputation and analysis model in both MI and RI methods, the Reed1 model was also fitted to complete data (CCA) and incomplete data (ACA), using linear mixed effects (LME) modelling as outlined in Figure 3.2.

Covariates such as maternal height, parity and socio-economic status (SES) were used in the multiple imputation of growth measurements. The SES variable was derived from several household characteristic variables such as type of housing, household assets, and paternal occupation.

To compare the 3 different methods of dealing with missing data MI, ACA or Regression Imputation (RI), the parameter estimates of the growth model for each method were compared with their corresponding parameter estimates from the original complete data (CCA). For the second component (which used actual missing data), parameter estimates from MI or regression imputation were compared with those from the ACA method.

The model parameter estimates were evaluated for bias in estimation. In general, bias is defined as:

Bias= $\text{E}(\hat{\theta}) - \theta$ where θ is the parameter of interest and is being estimated by $\hat{\theta}$.

The comparison was done using Relative Bias (RBIAS) of the growth model coefficients and the root of relative mean square errors (RRMSE) as defined in He et al. (He, 2010).

Relative bias is defined as RBIAS= |Bias/True| * 100%

where Bias= Coeff (Method) - Coeff (True).

Coeff (True) represented model coefficients derived from Complete Case Analysis, while Coeff (Method) represented model coefficients derived from MI, ACA or Regression imputation.

The root of the relative mean square error is defined as RRMSE= $\sqrt{MSE(Method)/MSE(True)}$.

The average of the relative biases and RRMSE were calculated from the 50 data sets. The percentage coverage, which looked at the proportion of parameters from the 50 datasets, that were within a 95 % confidence interval of their corresponding estimates derived from complete data (CCA), were also used to compare the different methods of dealing with missing data. Paired t-tests were used to compare the observed, interpolated and multiple imputed weight and height measurements.

STUDY METHODOLOGY FLOW CHART (for the simulated missing data component). (Adapted from Peters S.A.E, et al.).

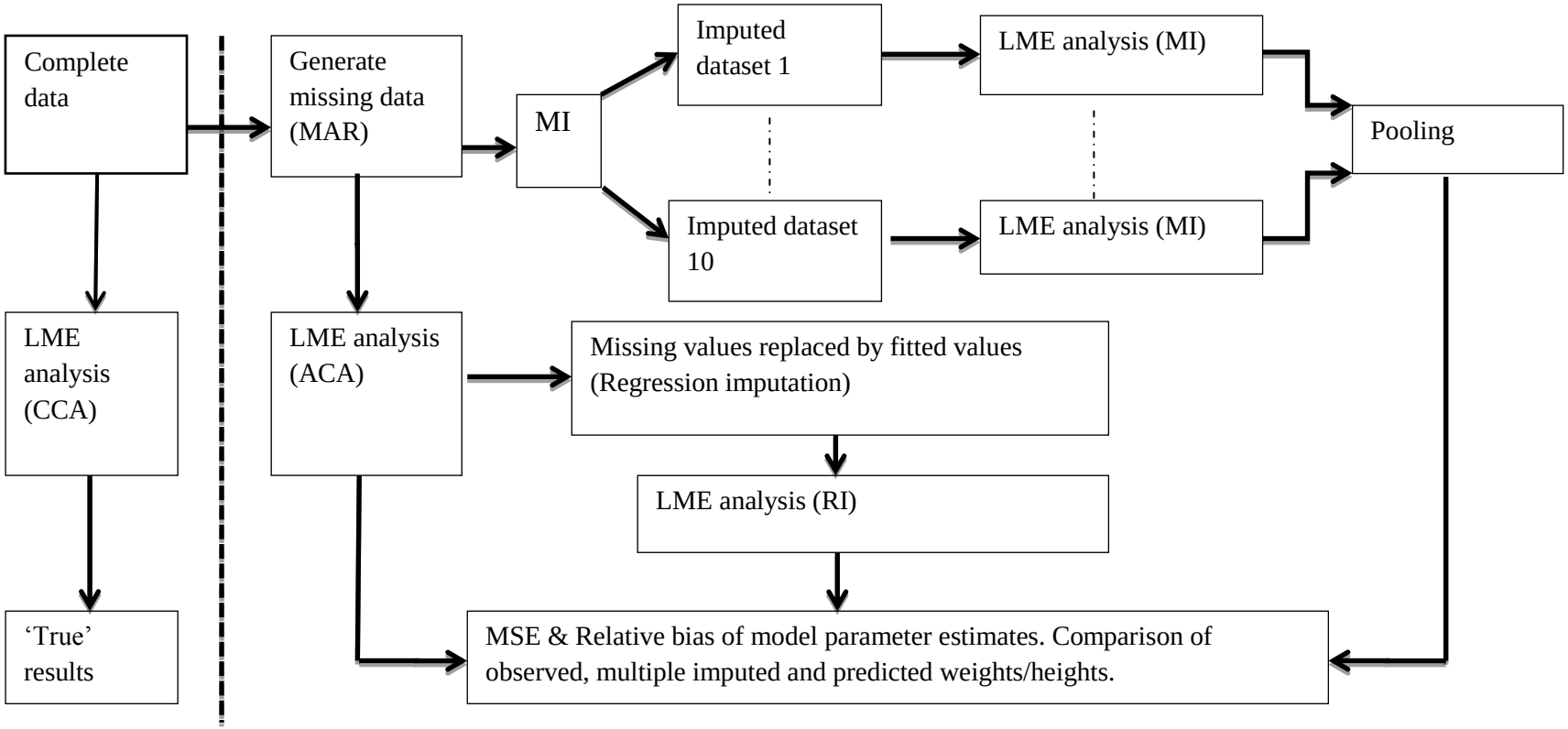


Figure 3.2 Methodology flow chart for simulated missing data

Abbreviations: LME=linear mixed effects; MCAR=missing completely at random; MI= Multiple Imputations; CCA= Complete Case Analysis; ACA= Available Case Analysis; MSE= Mean square error; RI=Regression Imputation.

N.B: Analysis done using Stata Version 13.

STUDY METHODOLOGY FLOW CHART (for the actual missing data component). (Adapted from Peters S.A.E, et al.).

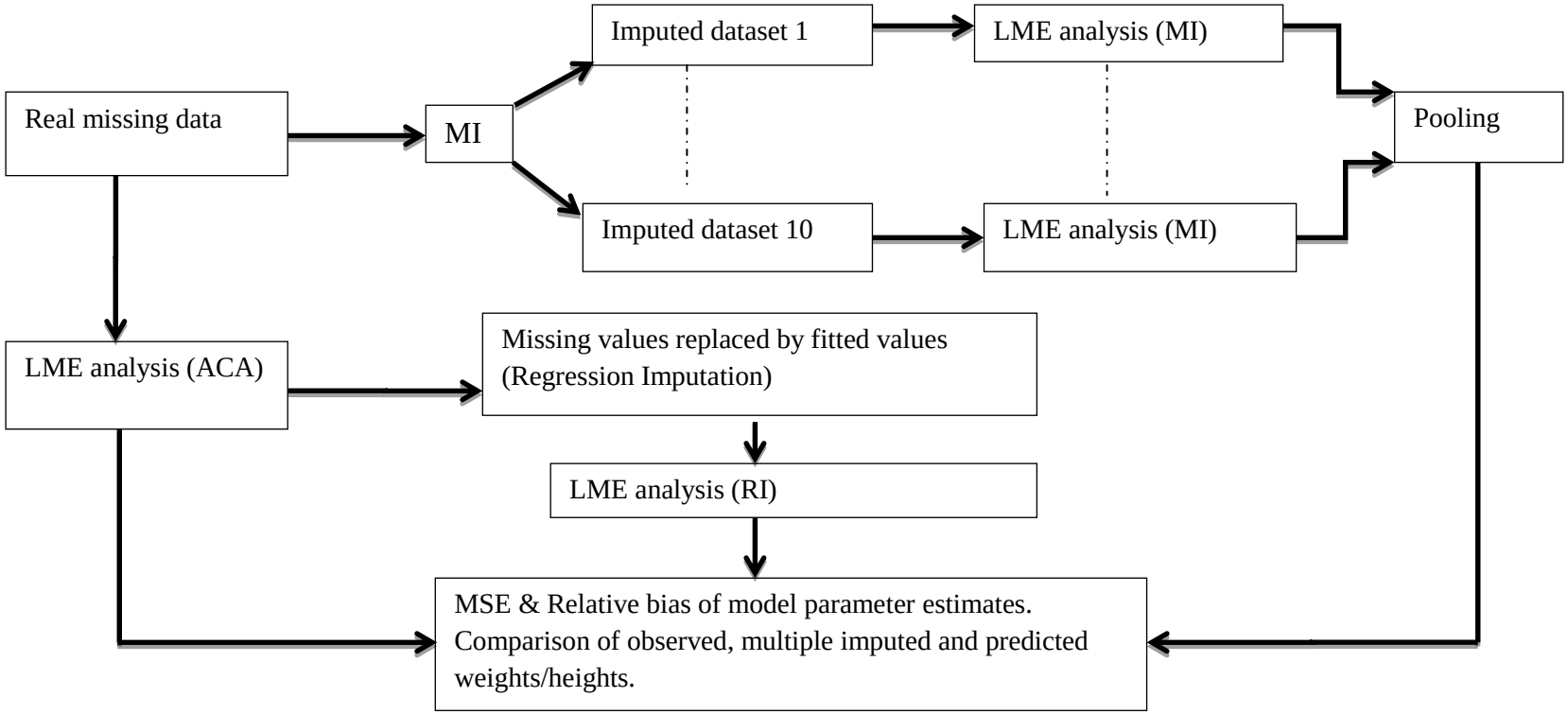


Figure 3.3 Methodology flow chart for actual missing data

Abbreviations: LME= linear mixed effects; MCAR= missing completely at random; MI= Multiple Imputations; CCA=Complete Case Analysis; ACA= Available Case Analysis; MSE= Mean square error; RI= Regression Imputation.

N.B: Analysis done using Stata Version 13.

3.3.3 Comparison of growth velocity in childhood and relationship with obesity

This sub-section outlines the methodology used in the selection of the analysis sample and the statistical methods used in the analysis of the final component of the PhD study. This final component compared growth velocity and examined the relationship between postnatal growth and early adolescent obesity in the 2 African cohorts.

3.3.3.1 Subjects and Methods

This component of the study used all participants from the 2 cohorts that had a sufficient number of data points for fitting the Reed1 model. The exclusion criteria and the overall number of participants available for analysis are shown in Fig 3.4.

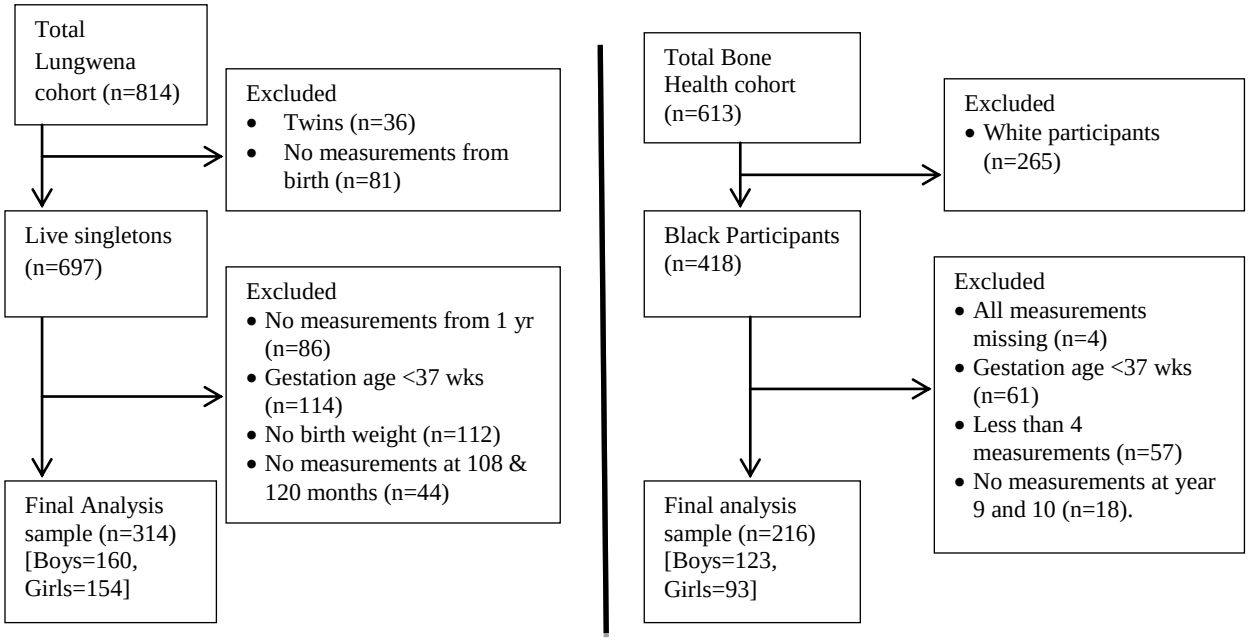


Figure 3.4 Flowchart of the analysis samples of the two cohorts

Due to differences in the socio-economic status (SES) measures collected in the two cohorts, a separate SES score was calculated for each cohort. SES measures in the Bone Health (BH) cohort included the following household assets: fridge, car, TV and washing machine, and the following household facilities: electricity, type of water system and toilet type. In the Lungwena cohort, SES measures included the following household assets: land ownership, bicycle, farm animals, and radio amongst others. Included also were household variables such as paternal and maternal education level. An asset score was initially derived based on household assets and principal component analysis was then used to derive an overall SES score by combining the asset score with other community and household SES measures.

The Reed1 model (Berkey, 1982) was fitted using mixed effects modelling. The model has the functional form;

$$y = \beta_0 + \beta_1 t + \beta_2 ln\,(t) + \beta_3 / (t). \quad (13)$$

The model (equation13) was modified as suggested by Simondon et al. , , so that it is defined at birth (t=0) as shown in equation (14) (Simondon et al., 1992):

$$y = \beta_0 + \beta_1 t + \beta_2 ln\,(t+1) + \beta_3 / (t+1). \quad (14)$$

The BR model was used to describe growth patterns in early childhood after adjusting for maternal characteristics (maternal height and age), SES and gestational age. Due to known differences in growth between boys and girls and due to perceived cohort differences, separate models were fitted for girls and boys in each cohort. The first order derivative of the model (equation 15) was then used to calculate weight and height velocities over time.

$$\frac{dy}{dt} = \beta_1 + \frac{\beta_2}{t+1} - \frac{\beta_3}{(t+1)^2} = \text{h (v)} \quad (15)$$

Peak weight velocity (PWV) and peak height velocity (PHV), age at peak weight velocity (APWV) and age at peak height velocity (APHV) were then derived from the growth velocity function (h(v)).

APWV was defined as $\frac{dh(v)}{dt} = 0$. Using the function h (v), the age at peak velocity was in turn used to calculate peak velocity.

The main outcomes of this part of the study were BMI and the proportion of overweight children in the 9-11 year age group. Corresponding overweight cut-offs were derived using BMI cut-off charts for children (Cole et al., 2000, Cole et al., 2007).

The derived model parameter estimates, weight and height growth velocity, infant peak weight and height velocity, and the age at peak velocity were used as predictors of adolescent BMI. Comparison of weight, height growth velocity, peak growth velocity between boys and girls within and between cohorts was done used t-tests after checking for normality assumptions. The relationship between BMI-for-age z-scores (BMIZ) in late childhood and early adolescence (9-11 years) and predictors, adjusting for cohort and sex differences, was examined using linear regression and predictors of obesity were explored using logistic regression. All analysis was done using Stata Version 11 with all statistical tests being performed at 5% significance level.

PART 3: EXPERIMENTAL PAPERS AND SUPPLEMENTARY RESULTS

Part 3 of the thesis also consists of three chapters. These chapters have been ordered according to the 4 broad objectives of the thesis. Chapter 4 compares the various growth models fitted to the 2 cohorts, while Chapter 5 looks at methods of dealing with missing data in weight and height measurements. Chapter 6 deals with the empirical research objective of the thesis, and compares child growth in the 2 cohorts and examines the relationship between early postnatal growth and early adolescent obesity.

CHAPTER 4: CHILD GROWTH CURVE MODELLING

This chapter deals with initial statistical modelling of the physical growth measurements in the two cohorts as outlined in the first objective of the thesis. The chapter includes a paper publication based on the BT 20 cohort (Section 4.1), supplementary results from modelling the BT 20 cohort (Section 4.2), and results from fitting the growth curve to the Lungwena cohort (Section 4.3). The original paper publication has also been included in Appendix 1.

4.1 PAPER 1

Title: Multilevel modelling of longitudinal child growth data from the Birth To Twenty cohort: A comparison of growth models.

Published in the

Annals of Human Biology, March 2014; 41(2): 168–179

INTRODUCTION

Human growth, like most developmental processes is complex. Human physical growth in length and weight is generally characterised by rapid growth in early life, followed by a general deceleration in childhood and then a marked increase in late childhood associated with the onset of puberty (Grimm et al., 2011, Karlberg, 1987, Pan and Goldstein, 1998). Growth models have been used in various disciplines to understand and capture general features of growth processes. They have extensively been used in developmental research to understand biological as well as psychological processes at the individual or population level, using data collected longitudinally (Black and Krishnakumar, 1999, Botton et al., 2008, Ehrenkranz et al., 1999, Grimm et al., 2011, Nguyen et al., 2012, Olusanya and Renner, 2011, Skinner et al., 2004).

Modelling of such longitudinal growth data involves fitting a model that best describes the changes in the growth measurements of an individual or population over time (Goldstein et al., 2002, Pan and Goldstein, 1998). The fitted models can be used to summarize and interpolate the pattern of growth in between measurement occasions and also identify critical periods in the growth process (Hauspie et al., 2004). Researchers have thus used growth models that can capture the nonlinearity of the growth process.

Researchers have over the years developed and used several growth models. These can broadly be classified into two groups, namely structural (or parametric) and non-structural (non-parametric) models (Hauspie et al., 2004). Common structural models used include the Jenss-Bayley model, the Count model, Berkey-Reed 1st and 2nd order models, the Infant-Childhood-Puberty (ICP) model, the Preece-Baines model and the Gompertz, while most common non-structural models are polynomials and splines (Gasser and Molinari, 2004, Hauspie et al., 2004, Olusanya and Renner, 2011, Pan and Goldstein, 1998, Botton et al.,

2008). The best model to describe the human growth process, be it at individual or population level, depends on the dimensions used (weight, height, skinfold or circumferences), the frequency of the measurements (weekly, monthly, yearly) and the period of growth being investigated (infancy, childhood or adolescence) (Hauspie et al., 2004, Karlberg, 1987). Growth models that have fitted well to the infancy or childhood period include the Jenss-Bayley, the Berkey-Reed and the Count models (Hauspie et al., 2004). All of these models have functions that capture the rapid growth and then subsequent deceleration that takes place during this period of growth. The ICP model summarises human growth into 3 overlapping components. The infancy component (birth to around 3 years) is an extension of the foetal stage, is predominantly affected by maternal and nutritional factors. The childhood component is from 1 year to around 11 years, and is predominantly controlled by growth hormones. Simondon and colleagues used the first component of the ICP model to describe growth from birth to 13 months in Congolese infants (Simondon et al., 1992).

Although non-structural models are easy to fit, they tend to be unstable at the extremities, and do not define any particular form of the growth curve and as such, their parameters do not have any biological interpretation (Hauspie et al., 2004, Singer and Willett, 2003).

There are several studies that have looked at child growth in low-and middle-income countries, but few have used longitudinal data, due to the limited number of longitudinal studies(Adair et al., 2009, Cameron et al., 1986, Fetuga et al., 2011, Guedes et al., 2010, Hauspie and Pagezy, 1989, Johnson et al., 2012b, Kalanda et al., 2005b, Maleta et al., 2003b, Mushtaq et al., 2012, Olusanya and Renner, 2011, Pagezy and Hauspie, 1985, Simondon et al., 1992, Stein et al., 2010).

A number of studies have used the quadratic curve or some structural human growth models to model early child growth data. Table 4.1 shows a summary of some of these studies and the models used. Of these studies, only 3 compared several models to find one that best described the particular population. Furthermore, very few studies have used structural or non-structural models on African longitudinal growth data (Cameron et al., 1986, Olusanya and Renner, 2011, Pagezy and Hauspie, 1985, Simondon et al., 1992). Previous studies done in this setting have also not considered the whole of the childhood period from birth to age 10 years. Apart from differences in the period to which the models have been fitted, these studies fitted models to each individual child separately (Cameron et al., 1986, Hauspie and Pagezy, 1989, Pagezy and Hauspie, 1985, Simondon et al., 1992). This study aims to compare models that have previously been predominately used to model infant and early childhood growth such as the quadratic and Berkey-Reed model and those used in late childhood period, such as the Jenss-Bayley and the adapted Jenss-Bayley models. This study aims to fit the models to the population growth data using mixed effects modelling. The rationale behind population-based growth modelling is that while different individuals are quantitatively different, their growth over time has a similar shape. Thus the objective of fitting a growth curve in this instance is to quantify this common shape, but at the same time take account of the between-individual differences in growth. As well as fitting individual curves, mixed effects modelling allows for fitting of a general population curve. The fixed part of a mixed model summarises the mean structure (general population curve), and the random component of the model allows for variations in individual growth of the children. The other advantage of using mixed effects models is that they allow for modelling of longitudinal data which have a different number of measurement occasions, or where some individuals have missing outcome measurements at some points, or have unequal spaced intervals between measurements occasions. The importance of this flexibility in the analyses

of longitudinal studies, where missing data are inevitable and where measurements on participants are more likely to be taken at the different times, can therefore not be emphasised. Mixed effects modelling also allows for inclusion of covariates that affect growth (Johnson et al., 2012b).

This study aims to compare four structural and two non-structural models that have been shown to fit well to the infant and childhood stage in high income country settings, by applying them to data from a South African (middle-income country) cohort. The objective of this study is to find a growth model that best describes physical growth of normal children from birth to ten years in this setting using mixed effects modelling techniques.

Table 4.1 Summary of studies that have used structural and non-structural models ‡.

	Authors	Study Population	Model(s) used	Period of growth	Variable
1	(Black and Krishnakumar, 1999)	USA (92% African-American)	Quadratic	0-6yrs	height, weight
2	(Ehrenkranz et al., 1999)	USA	Piece-wise quadratic	0-6 months	Weight
3	(Martin-Gonzalez et al., 2012)	Spanish and Siberian	Kouchi	Birth-6 years	height
4	(Grimm et al., 2011)	USA	Linear; Quadratic; Latent basis model, Preece-Baines	3-19 years	height
5	(Johnson et al., 2012b)	Indian	Berkey-Reed 1 st order; Count; Quadratic	0-15 months	weight
6	(Botton et al., 2008)	French	Adapted Jenns- Bayley model (with a quadratic term)	0-12 years	weight, height
7	(Simondon et al., 1992)	Congolese (African)	Berkey-Reed 1st order; Count; Karlberg; Berkey-Reed 2nd order; Kouchi	0-13 months	Weight
8	(Tilling et al., 2011)	Belarus	Fractional Polynomial	0-6.5 years	Weight, height
9	(Flexeder et al., 2012)	German	Berkey-Reed 1st order	0-2 years	Weight, height
10	(Steele, 2008)	British	3rd Order Polynomial (cubic)	11-14 years	Height

‡ **Publications found using Pubmed and Google-Scholar search**
Search terms used: mathematical growth curve, child growth models, human growth model,

SUBJECTS AND METHODS

The study used weight and height measurements from 453 participants of the Bone-Health (BH) study as outcome variables. The BH Study is a sub-sample of the Birth-to-Twenty (Bt20) birth cohort set in Soweto-Johannesburg, South Africa. Of the 453 participants, 43 had a gestational age of less than 37 weeks (term) and were excluded from the analysis. The data comprised of anthropometric measurements at birth, 3 months, 6 months, 1 year, 2 years, 4 years, 5 years, 7/8 years, 9 years and at 10 years. All participants whose weight-for age z-scores (WAZ) or whose height-for-age were consistently (on at least 3 occasions) greater than +2 or less than -2 were excluded from analysis as these were considered outliers for growth within the context of the BH cohort population.

Only participants with at least 5 weight or height measurements were included in the study since the largest models have 4 parameters. Since height/length measurements were only taken from 3 months of age, there were 2 separate final 'analysis data sets' for modelling weight and height. The final 'analysis data set' for weight as outcome had 365 participants, while the one for height had 350 participants.

Growth Curve modelling

Before fitting the growth curve, descriptive statistics such as means, standard deviations, and frequencies were calculated. T-tests were used to compare mean weights and heights at each measurement occasion. These comparisons were done on both the overall data set and the final 'analysis data set'. Proportions of males, small for gestation age (SGAs) and firstborns in the overall data set were also compared to those in the final 'analysis data set' to see whether there were any differences in characteristics between the two datasets. Exclusion of children with less than 5 measurements did not affect the general population distribution by sex, parity or mean maternal age. Several growth models were fitted to the data using a mixed effects modelling approach. The sex of a participant was entered as a covariate to take into account known difference in growth between males and females. The study also explored any interaction between sex and age of a child. To be able to fit the growth models as linear models, other functions of the variable 'age' such as natural log of age , ln(age), and exponential of age were calculated. A summary of modelling procedure is outlined in 3.2.1.3.

RESULTS

Descriptive statistics

Of the 365 participants used in modelling weight, 190 (52%) were males, 139 (44%) were first born and 25 (6.9%) had small birth weight for their gestation age (SGA), and the mean age of the mother was 25.1 years (SD=6.1).

Comparisons of the mean weight and height measurements by sex or birth weight [SGA vs appropriate for gestation age (AGA)] were made at each measurement occasion (results not shown). There were slight differences in average weight and height from birth to about 2 years between AGA and SGA infants, indicating smaller babies gaining weight and height faster ($0.05<p<0.10$).

In line with biological expectations, there was significant difference in average weight and height between males and females at most of the measurement occasions, especially during the early years, with boys weighing on average more than girls and also being taller than girls. There were significant differences in average weight between boys and girls from birth to 1 year. Similar trends were observed in mean height between the two sexes from 3 months to around 2 years, with boys being on average taller than girls. There were no significant differences in mean weight or height between boys and girls from 2 years to around 9 years. At 10 years, the girls were on average heavier than boys, though the difference was not significant.

Weight and height profiles for a random sample of boys and girls have been shown in the first graphs of Figures 4.1 and 4.2. The weight profiles show some rapid weight gain in the first year of life. A similar trend is shown by the height profiles.

Fitted growth models for weight of children.

The parametric growth curve functions used were the Berkey-Reed 1st and 2nd order model, the Count model, Jenss-Bailey model and the adapted Jenss-Bayley model. The non-structural models fitted were the 2nd and 3rd order polynomials. The Berkey-Reed 2nd order model was highly correlated with its 1st order model. Thus, the 1st order which has fewer parameters was used in the modelling, considering that the number of measurement occasions per child was also small. There were significance effects of adding the random intercepts to models with 'sex-age interactions' for all growth functions (all p-values <0.05). Only age was included in the random component of all of the models, since the addition of higher order functions of age led to non-convergence of the models.

The graphical representations of the fitted curves on the observed weight are shown in Figure 4.1. The Berkey-Reed 1st order model had the best fit at all of the measurement occasions, with the curves passing almost at the middle of the observed measurements at each time point (except at 3 months). The Count and the 3rd order Polynomial models also fitted well at most of the measurement occasions. All of the models except for the Berkey-Reed 1st order model do not fit well to the first 4 measurement occasions (birth to 1 year). The 3rd order Polynomial picks up the rapid weight gain from around 9 years, while the other 4 models are approximately linear and do not allow for this weight gain.

The findings from the graphical representation were also supported by the percentage of positive raw residuals at each measurement occasion (Table 4.2), with close to 50% positive residuals at each measurement occasion being an indication of a good fitting model.

From Table 4.2, the quadratic, the adapted Jenss-Bayley and Jenss-Bayley models had no positive residuals at birth, implying that all predicted birth weights were higher than the observed birth weights. Apart from the Berkey-Reed model, the other models had a poor fit

at birth. At year 1, all 6 models did not fit well, with more than 80% of the residuals being positive. In general the Jenss-Bayley and quadratic models had a poor fit from birth to 2 years but fitted better in later years, while the 3rd order Polynomial, the Count and the adapted Jenss-Bayley did not fit well up to around 1 year.

Although the percentages of positive residuals from fitting a Berkey-Reed model were consistently close to 50% at most of the measurement occasions, the model fitted poorly at 3 months and at 7/8 years. At 3 months, only 6 % of predicted weights were less than the observed weight, while at 7/8 years, 80% of the predicted weights were less than the observed. This was also shown by the large median and maximum absolute residuals.

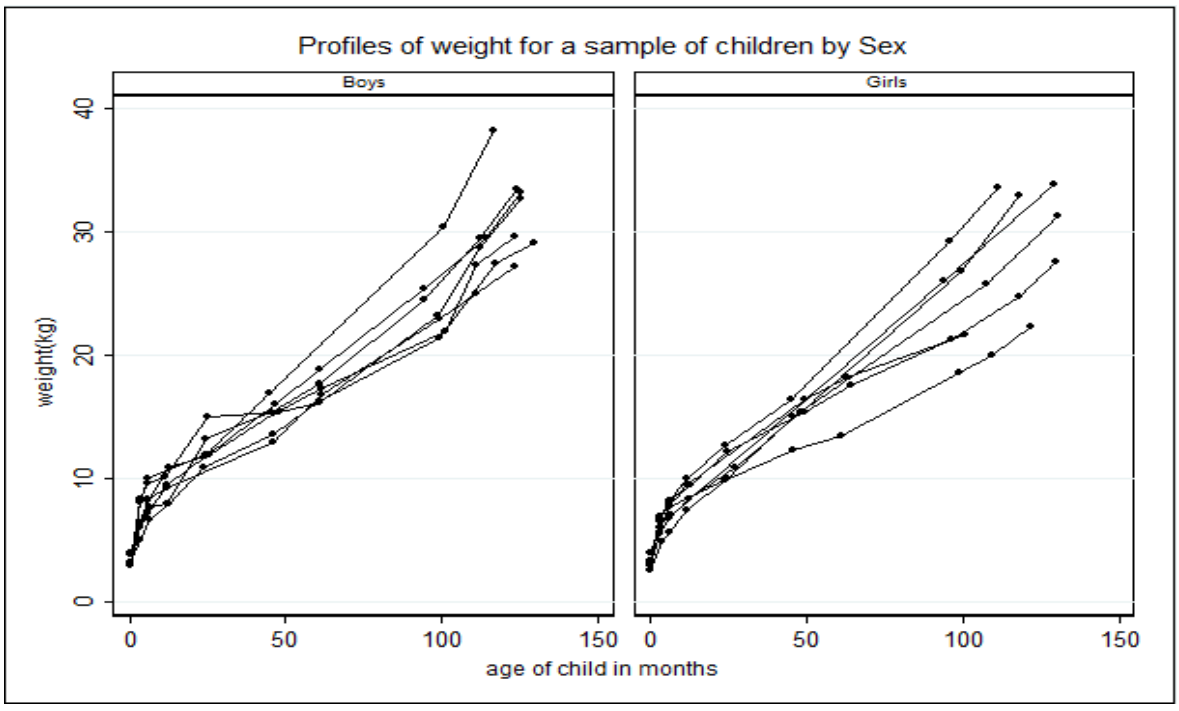


Figure 4.1 Weight profiles for a sample of boys and girls.

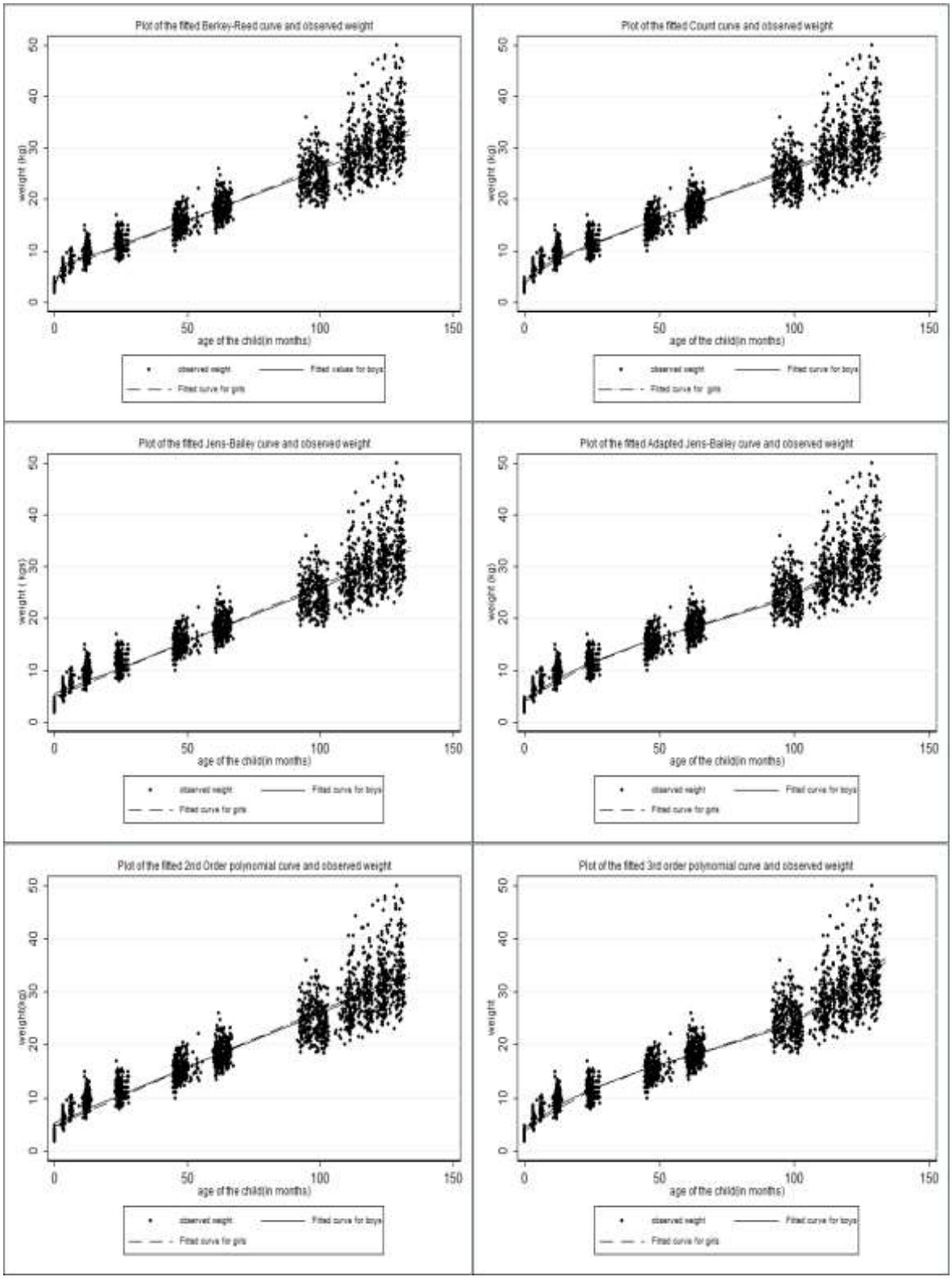


Figure 4.2 Growth models fitted to weight measurements.

Both the adapted Jenss-Bayley and the 3rd order polynomial also did not fit well from birth to around 1 year, but fitted better in the later years. Based on the overall trend in percentage of positive residuals, it can be concluded that the Berkey-Reed model fits better than the other 5 models.

The random intercept (σ^2_{u0}) represents the variation in the initial value. For models fitted from birth, the initial value represents the birth weight of a child. The random intercept allows for estimation of an individual child's birth weight, thus the model does not constrain individuals to have the same birth weight. The random slope (σ^2_{u1}) in the models allows for the estimation of differences in individual growth trajectories, linear in age. The results in Table 2 show that the variances (σ^2_{u0}) for the random intercept ranged from 0.001 to 0.245, with the 3rd order Polynomial model having the largest variance estimate and the Jenss-Bayley having the largest standard error of the estimate. But the confidence intervals for σ^2_{u0} for all the models overlapped, indicating that there were no significant differences in the random intercepts of the 6 fitted growth curves. All models had similar estimates of variance (σ^2_{u1}=0.001) of the random slope and similar standard errors.

The estimates for the covariance ($\sigma_{u0}\ \sigma_{u1}$) of the intercept and slope in all of the 6 models were all negative. Although the covariance estimates for all the models are also negative, most of the confidence intervals included zero, indicating a non-significant negative covariance. Only the 3rd order polynomial model had a significant negative covariance. A significant negative covariance indicates that those with low initial values (low birth weight) grow faster than those with higher initial values (normal/large babies).

The estimates for the effects of sex differences on weight, ranged from -0.44 to -0.53, showing that girls were on average about half a kilogram lighter than boys. The 95% confidence limits ranged from -0.75 to -0.26, indicating that differences in weight between weight of boys and girls range from approximately 300g to 800g.The confidence intervals for the effect of sex in all of the models overlapped, again indicating that there is no significant difference in the estimation of the effect by the 6 models (Table 4.2).

The effect of age and sex interaction was significant in all the 6 models. The estimate for this effect for all the 6 models was 0.01, indicating an average monthly increase of 10g in girls relative to boys. All terms which are a function of age of the participant, in all the models were highly significant ($p < 0.001$). This shows the importance of applying the different functions of age to appropriately model the shape of a growth curve.

Goodness of fit tests for models on weight.

The Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), median and maximum values of absolute residuals and the variance (σ_ε^2) of residuals were used to assess the goodness of fit of all of the models (Table 4.3). For all the goodness of fit statistics, the smaller the value of the statistics, the better the model is fitting to the data.

Both the Berkey-Reed and the 3rd order Polynomial models had the smallest AIC and BIC values (10758 and 10811 respectively), and the Berkey-Reed had the smallest overall median absolute residual of 0.62 with interquartile range of 0.28 to 1.20. It also had consistently the smallest median of the absolute residuals at most of the 10 measurement

occasions. The maximum values for the absolute residuals for the 6 models range from 7.16 to 8.80, with the 3rd order Polynomial model having the smallest maximum value.

The ranks of the AIC, BIC, and the median and maximum absolute residual values show the Berkey-Reed having the smallest sum of the ranks, with 17 out of 25 ranks for the model being less than 3. The Kruskal-Wallis test on the ranks of the goodness of fit statistics showed significant differences in the ranks ($p<0.001$) and the Berkey-Reed model had the smallest rank sum, followed by the 3rd order polynomial model.

Although there were no significant differences in the values of the median absolute residuals ($p=0.59$), the Berkey-Reed model had the smallest sum of the ranks, indicating that the model had consistently smaller median absolute residuals at all of the measurement occasions. Similarly there were no significant differences in the sum of the ranks of the maximum absolute residual values amongst the models ($p=0.92$), but the Berkey-Reed model had the smallest rank sum, again indicating consistently smaller values of absolute residuals for this model.

The estimates of the variance (σ_{ε}^2) of residuals after fitting the models to the data ranged from 1.95 to 3.06, with the 3rd order Polynomial model having the smallest value and the Jenss-Bayley model, the largest value.

Table 4.2 Parameter estimates for models fitted to weight and height measurements.

		Weight			Height		
Model	Coefficient	Estimate	Std. Error	95 % Confidence Interval	Estimate	Std. Error	95 % Confidence Interval
Reed1	Intercept	7.31	0.177	(6.96, 7.66)	43.15	0.962	(41.27, 45.04)
	age	0.20	0.003	(0.19, 0.21)	0.37	0.005	(0.36, 0.38)
	Ln(age)	-0.37	0.069	(-0.51, -0.24)	9.90	0.296	(9.32, 10.48)
	1/age	-0.006	0.0006	(-0.008, -0.005)	15.17	2.256	(10.75, 19.59)
	Females	-0.53	0.092	(-0.71, -0.34)	-1.67	0.315	(-2.29, -1.06)
	Female*age	0.010	0.004	(0.002, 0.017)	0.02	0.005	(0.01, 0.03)
Count	Intercept	3.88	0.091	(3.70, 4.05)	45.99	0.377	(45.26, 46.73)
	Age	0.18	0.003	(0.17, 0.19)	0.38	0.004	(0.37, 0.39)
	Ln(age+1)	0.94	0.037	(0.87, 1.01)	9.02	0.123	(8.78, 9.26)
	Females	-0.44	0.096	(-0.71, -0.32)	-1.67	0.314	(-2.29, -1.06)
	Female*age	0.01	0.004	(0.001, 0.017)	0.02	0.005	(0.01, 0.03)
Jenns-Bayley	Intercept	5.36	0.066	(5.23, 5.50)	79.89	0.511	(78.88, 80.90)
	Age	0.21	0.003	(0.207, 0.215)	0.47	0.005	(0.46, 0.48)
	Exp(const)	-6.20	0.006	(-6.21, -6.19)	3.14	0.017	(3.10, 3.17)
	Exp(age)	0.008	0.044	(-0.079, 0.095)	-0.049	0.002	(-0.053, -0.045)
	Females	-0.46	0.102	(-0.66, -0.26)	-1.49	0.323	(-2.13, -0.86)
	Female*age	0.01	0.004	(0.001, 0.016)	0.02	0.005	(0.01, 0.03)
Adapted Jenss-Bayley	Intercept	5.25	0.082	(5.09, 5.41)	66.89	0.468	(65.97, 67.81)
	Age	0.22	0.003	(0.21, 0.23)	0.75	0.012	(0.72, 0.77)
	$(Age)^2$	-0.0001	0.00002	(-0.0001, -0.00002)	-0.001	0.0001	(-0.0016, -0.0013)
	Exp(const)	-33.00	0.011	(-33.02, -32.98)	2.76	0.047	(2.76, 2.86)
	Exp(age)	0.14	1.399	(-2.61, 2.89)	-0.18	0.019	(-0.22, -0.14)
	Females	-0.53	0.102	(-0.73, -0.34)	-1.51	0.318	(-2.14, -0.89)
	Female*age	0.01	0.003	(0.002, 0.016)	0.02	0.005	(0.01, 0.03)
2^{nd} Order Polynomial	Intercept	5.28	0.083	(5.12, 5.45)	62.37	0.258	(61.86, 62.88)
	Age)	0.21	0.004	(0.20, 0.22)	0.88	0.007	(0.86, 0.89)
	$(Age)^2$	-0.00007	0.00002	(-0.0001, -0.00003)	-0.002	0.00004	(-0.0024, -0.0022)
	Females	-0.54	0.107	(-0.75, -0.33)	-1.63	0.343	(-2.30, -0.95)
	Female*age	0.01	0.004	(0.002, 0.018)	0.02	0.005	(0.01, 0.03)
3^{rd} Order Polynomial	Intercept	4.34	0.081	(4.18, 4.50)	59.47	0.268	(58.95, 59.91)
	Age	0.38	0.006	(0.37, 0.39)	1.17	0.012	(1.15, 1.19)
	$(Age)^2$	-0.004	0.0001	(-0.004, -0.0036)	-0.0079	0.0002	(-0.008, -0.007)
	$(Age)^3$	0.00002	6e-06	(0.000019, 0.000022)	0.00003	1e-06	(0.000027, 0.000031)
	Females	-0.53	0.101	(-0.73, -0.33)	-1.65	0.325	(-2.29, -1.02)
	Female*age	0.01	0.003	(0.002, 0.016)	0.02	0.005	(0.01, 0.03)

Table 4.3 Goodness of Fit statistics for models fitted to weight measurements.

		Berkey-Reed 1	Count	Jenss-Bayley	Adapted Jenss-Bayley	2nd Order Polynomial	3rd Order Polynomial
Variance Components[#]	Random Intercept	0.160(0.072, 0.355)	0.117(0.035,0.389)	0.008(-0.173, 0.188)	0.008(-0.17, 0.181)	0.005(0.0001, 0.166)	0.249(0.142, 0.436)
	Random Slope	0.0013(0.001, 0.002)	0.0013(0.001, 0.002)	0.0013(0.001, 0.002)	0.0013(0.001, 0.0014)	0.001(0.0010, 0.002)	0.0013(0.001. 0.002)
	Covariance	-0.002(-0.006, 0.001)	-0.003(-0.007, 0.001)	-0.002(-0.006, 0.003)	-0.002(-0.006, 0.003)	-0.002(-0.007, 0.002)	-0.005(-0.01, -0.0006)
	Random Residuals	1.98(1.86, 2.10)	2.35(2.02, 2.50)	3.06(2.87, 3.25)	3.05(2.87, 3.23)	3.051(2.87, 3.24)	1.95(1.83, 2.07)
Information Criterion	AIC	10758	11127	11704	11693	11684	10758
	BIC	10811	11175	11739	11724	11708	10811
Absolute Residuals[†*]	Median	0.62(0.28, 1.20)	0.72(0.33, 1.35)	0.99(0.44, 1.89)	0.99(0.44, 1.84)	0.99(0.44, 1.84)	0.86(0.42, 1.37)
	Maximum	8.46	8.80	8.53	8.66	8.66	7.16
Median Absolute Residuals[‡*]	Birth(n=365)	0.32(0.15, 0.54)	0.54(0.27, 0.83)	2.03(1.70, 2.37)	1.90(1.59, 2.26)	1.91(1.59, 2.25)	0.99(0.67, 1.30)
	3m(n=126)	1.14(0.76, 1.57)	0.61(0.30, 1.05)	0.58(0.31, 0.90)	0.58(0.34, 0.99)	0.58(0.34, 0.99)	0.72(0.47, 1.14)
	6m(n=87)	0.55(0.31, 0.89)	1.18(0.55, 1.66)	1.34(0.77, 1.96)	1.41(0.84, 2.03)	1.42(0.84, 2.03)	1.47(0.82, 1.82)
	Year 1(n=270)	0.85(0.34, 1.44)	1.19(0.55, 1.82)	1.74(1.00, 2.53)	1.77(1.02, 2.55)	1.77(1.02, 2.56)	1.20(0.55, 1.72)
	Year 2(n=264)	0.79(0.38, 1.43)	0.82(0.39, 1.41)	1.16(0.52, 1.94)	1.13(0.51, 1.90)	1.13(0.51, 1.90)	0.77(0.38, 1.22)
	Year 4(n=345)	0.65(0.32, 1.18)	0.76(0.32, 1.30)	0.74(0.35, 1.34)	0.73(0.35, 1.31)	0.73(0.35, 1.31)	0.76(0.35, 1.33)
	Year 5(n=306)	0.63(0.25, 1.09)	0.73(0.34, 1.26)	0.60(0.25, 1.12)	0.66(0.25, 1.11)	0.66(0.25, 1.11)	0.59(0.30, 1.04)
	Year 7/8(n=322)	0.76(0.35, 1.74)	0.83(0.39, 1.83)	0.87(0.40, 1.85)	0.92(0.44, 1.89)	0.92(0.44, 1.89)	0.93(0.48, 1.41)
	Year 9(n=299)	0.48(0.23, 0.89)	0.45(0.23, 0.87)	0.63(0.29, 0.99)	0.60(0.29, 0.97)	0.60(0.29, 0.97)	0.51(0.23, 0.90)
	Year 10(n=313)	0.79(0.32, 1.68)	0.96(0.34, 1.94)	0.71(0.35, 1.51)	0.76(0.35, 1.61)	0.76(0.35, 1.61)	1.06(0.55, 1.57)
Maximum absolute residuals[‡]	Birth(n=365)	1.27	1.89	3.44	3.32	3.32	2.32
	3m(n=126)	3.54	2.62	2.60	2.70	2.71	2.61
	6m(n=87)	2.60	3.60	3.94	4.03	4.02	3.75
	Year 1(n=270)	5.57	6.25	6.97	7.01	7.01	6.00
	Year 2(n=264)	4.14	4.03	4.99	4.96	4.95	3.51
	Year 4(n=345)	6.33	6.77	6.10	6.24	6.24	6.85
	Year 5(n=306)	4.37	4.81	4.28	4.45	4.45	3.81
	Year 7/8(n=322)	7.31	7.40	7.25	7.32	7.32	6.18
	Year 9(n=299)	5.05	5.31	5.18	5.24	5.24	4.78
	Year 10(n=313)	8.45	8.80	8.53	8.66	8.66	7.16
Sum of the Rank		56	89.5	96	109	107	68.5
Kruskal-Wallis Rank Sum	P<0.001	1076	1956	2096	2423	2361	1412
% positive raw residuals	Birth(n=365)	174(48)	45(12)	**0(0)**	**0(0)**	0(0)	3(1)
	3m(n=126)	6(5)	96(76)	79(63)	89(71)	89(71)	110(87)
	6m(n=87)	51(59)	79(91)	81(93)	82(94)	82(94)	85(98)
	Year 1(n=270)	215(80)	241(89)	252(93)	257(95)	257(95)	243(90)
	Year 2(n=264)	166(63)	149(56)	214(81)	212(80)	212(80)	118(45)
	Year 4(n=345)	160(46)	106(31)	203(59)	182(53)	182(53)	97(28)
	Year 5(n=306)	139(45)	78(25)	163(53)	139(45)	139(45)	182(59)
	Year 7/8(n=322)	50(16)	41(13)	42(13)	35(11)	35(11)	211(66)
	Year 9(n=299)	115(38)	131(44)	88(29)	96(32)	96(32)	180(60)
	Year 10(n=313)	226(72)	264(84)	195(62)	205(65)	205(65)	103(33)

[†]: Distribution of absolute residuals for each model.

[‡]: Distribution of absolute residuals for each model at each measurement occasion.

[#]: Variance components are given with their 95% CI.

[*]: Medians are given with their Interquartile Range (IQR)

AIC:- Akaike Information Criterion

BIC: - Bayesian Information Criterion

Fitted growth models for height of children.

Figure 4.2 shows the graphical representation of the 6 models for height fitted from 3 months to 10 years, showing the Count, the adapted Jenss-Bayley and Berkey-Reed 1st order models fitting well to the data at almost all the measurement occasions. Table 4.4 also shows the percentage of positive residuals from fitting the 6 models. The percentage of positive residuals from fitting the adapted Jenss-Bayley or Berkey-Reed 1st order model is close to 50% at almost all the measurement occasions. All of the models, except the 3rd order Polynomial, did not fit well at year 2. They either overestimated (small % of positive residuals) or underestimated (large % of positive residuals). The adapted Jenss-Bayley did also not fit well at year 7/8, while the Jenss-Bayley model did not fit well at years 1 and 5. The 2nd order polynomial did not fit well at almost all points except at age 5 and 9 years. The 2nd and 3rd order polynomial models had very low percentage of positive residuals at 3 months, and a high percentage from year 1 to year 4, indicating overestimation at 3 months and underestimation from year 1 to year 4.

The estimates for variances (σ^2_{u0}) of the random intercepts (variation in height at 3 months) ranged from 6.25 to 6.82, with the Count model having the smallest estimate. But the confidence intervals for estimates of the random intercept (σ^2_{u0}) for all the models overlapped indicating that there were no significant differences in the estimation of random intercept between the different shapes of curves fitted across the models. The estimate of the covariance ($\sigma_{u0}\ \sigma_{u1}$) of the random intercept and slope for all the models were all positive, and not significantly different from each other (confidence intervals overlapped). All of the confidence intervals for the covariance estimates included zero, indicating independence

between one's initial height at 3 months (random intercept) and their growth rates (random slope). All of the models had similar estimates of variance (σ^2_{u1}) of the random slope, with overlapping confidence intervals.

The estimates for the effects of sex differences on height, ranged from -1.67 to -1.49, showing that girls were on average about 1.5 to 2.0 centimetres shorter than boys. The confidence intervals for the effect of sex in all the models overlapped, indicating that there were no significant differences in the estimates from the different models. The sex-age interaction estimate for all the models was 0.02, indicating an average monthly increase in girls' height of about 0.2mm relative to boys. From about 4 years to 7/8years, there were no differences in the average height between boys and girls. As with weight models, all terms which are a function of age of the participant, in all the models were highly significant (all p <0.001), indicating the relationship between physical growth and one's age.

Goodness of fit tests for models on height.

The AIC values ranged from 11510 to 12259, with the Berkey-Reed model having the smallest AIC and BIC values as well as the smallest estimates for the random residuals (σ^2_ε). The Count model also had smaller AIC and BIC values compared to the other 4 models. The overall median absolute residuals ranged from 0.90 to 1.11, with the adapted Jenss-Bayley having smallest overall median of absolute residuals, and the quadratic model having the largest value. All models did not fit well to the data at year 2, producing very large maximum absolute residuals. This is could be due to the wide variation in height measurements at this data collection waves. The height measurements ranged from 70cm to

95 cm for age that ranged from 22.5 to 28 months. The wide variation in the measurements could have been due to the changes in measurement procedure from sitting to standing positions. The Kruskal-Wallis test on all the ranks of the goodness of fit statistics showed significant differences in ranks, with the adapted Jenss-Bayley model having the smallest rank sum.

At each measurement occasion, the adapted Jenss-Bayley and the Berkey-Reed models have consistently smaller maximum and median values of absolute residuals. But the Kruskal-Wallis test on the maximum and median absolute values showed no significant differences (p-values of 0.57 and 0.72 respectively). But the adapted Jenss-Bayley had the smallest sum of ranks followed by the Berkey-Reed model.

Figure 4.3 Height profiles for a sample of boys and girls.

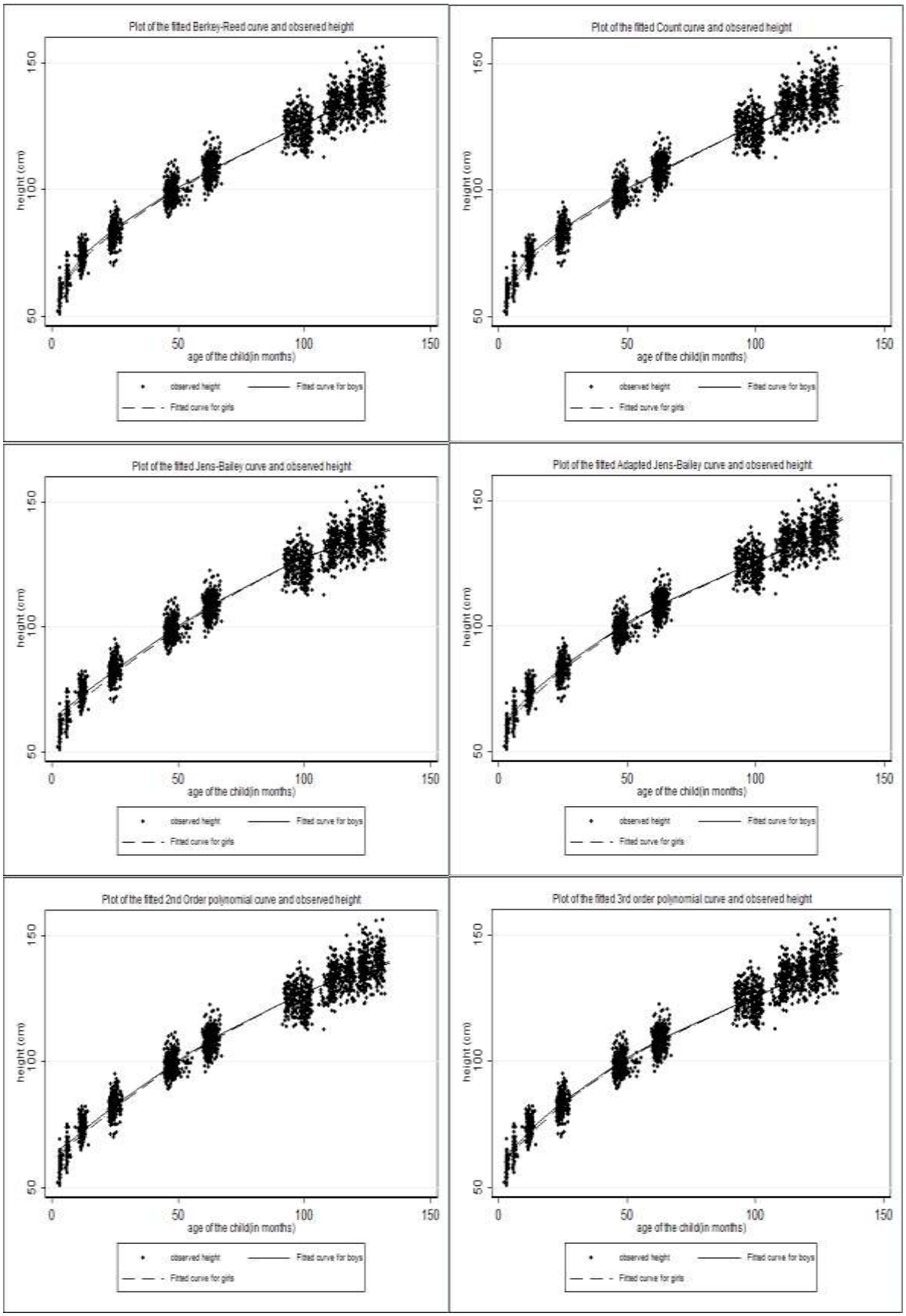


Figure 4.4 Growth models fitted to height measurements.

Table 4.4 Goodness of Fit statistics for models fitted to height measurements.

		Berkey-Reed 1	Count	Jenss-Bayley	Adapted Jenss-Bayley	2nd Order Polynomial	3rd Order Polynomial
Variance Components[#]	Random Intercept	6.32(5.14, 7.78)	6.25(5.08, 7.70)	6.45(5.10, 7.80)	6.21(4.91, 7.51)	6.78(5.40, 8.52)	6.65(5.39, 8.20)
	Random Slope	0.002(0.001, 0.0021)	0.002(0.001, 0.0021)	0.002(0.001, 0.0022)	0.002(0.001, 0.0022)	0.002(0.001, 0.0022)	0.002(0.001, 0.0021)
	Covariance	0.007(-0.008, 0.022)	0.007(-0.007, 0.022)	0.007(-0.008, 0.022)	0.007(-0.007, 0.023)	0.005(-0.011, 0.022)	0.006(-0.009, 0.022)
	Random Residuals	4.30(4.01, 4.60)	4.33(4.04, 4.64)	4.48(4.17, 4.78)	4.38(4.07, 4.68)	6.53(6.10, 7.00)	4.75(4.44, 5.09)
Information Criterion	AIC	11510	11519	11586	11539	12259	11696
	BIC	11562	11565	11620	11577	12305	11747
Absolute Residuals[†*]	Median	0.94(0.41, 1.75)	0.97(0.43, 1.80)	0.95(0.42, 1.80)	0.90(0.40, 1.69)	1.11(0.51, 2.09)	1.00(0.44, 1.86)
	Maximum	12.87	12.95	12.64	12.46	11.16	11.76
Median Absolute Residuals[‡*]	3m(n=119)	1.37(0.48, 2.37)	1.38(0.64, 2.37)	1.24(0.66, 2.50)	1.39(0.52, 2.36)	3.58(2.37, 5.20)	1.86(1.07, 3.44)
	6m(n=87)	1.31(0.68, 2.29)	1.23(0.51, 2.40)	1.34(0.78, 2.25)	1.20(0.52, 2.59)	1.29(0.57, 2.92)	1.24(0.56, 2.33)
	Year 1(n=259)	1.18(0.57, 1.95)	1.17(0.58, 1.90)	1.54(0.68, 2.40)	1.09(0.58, 2.01)	1.65(0.76, 2.81)	1.79(0.85, 2.83)
	Year 2(n=303)	1.32(0.59, 2.19)	1.34(0.62, 2.21)	1.19(0.54, 2.12)	1.08(0.51, 1.96)	1.22(0.55, 2.05)	0.95(0.38, 1.75)
	Year 4(n=336)	0.94(0.43, 1.59)	0.93(0.44, 1.64)	0.90(0.40, 1.58)	0.96(0.47, 1.78)	1.06(0.53, 1.80)	0.91(0.43, 1.66)
	Year 5(n=303)	1.09(0.45, 1.77)	1.17(0.51, 1.91)	0.98(0.43, 1.62)	0.96(0.44, 1.67)	0.83(0.37, 1.47)	0.80(0.39, 1.42)
	Year 7/8(n=314)	0.84(0.42, 2.14)	0.86(0.42, 2.13)	0.96(0.41, 2.20)	0.88(0.36, 2.33)	1.48(0.71, 2.86)	1.08(0.43, 2.37)
	Year 9(n=299)	0.52(0.25, 1.03)	0.53(0.25, 1.06)	0.54(0.24,1.06)	0.52(0.21, 0.99)	0.57(0.25, 1.01)	0.71(0.37, 1.32)
	Year 10(n=308)	0.81(0.31, 1.39)	0.84(0.33, 1.37)	0.82(0.31,1.38)	0.77(0.42, 1.35)	1.10(0.52, 1.85)	0.92(0.36, 1.58)
Maximum absolute residuals[‡]	3m(n=119)	6.98	6.53	8.08	6.81	11.16	9.37
	6m(n=87)	7.46	7.63	7.30	7.83	8.65	7.70
	Year 1(n=259)	5.32	5.05	6.15	4.96	6.89	6.71
	Year 2(n=303)	12.87	12.95	12.64	12.46	10.44	11.76
	Year 4(n=336)	5.80	5.67	6.01	5.71	6.24	6.58
	Year 5(n=303)	10.12	10.27	9.88	9.99	9.16	9.17
	Year 7/8(n=314)	6.78	6.73	6.64	7.47	8.27	6.33
	Year 9(n=299)	4.76	4.78	4.69	4.88	4.83	4.32
	Year 10(n=308)	9.55	9.47	9.45	10.26	11.09	8.89
Sum of the Ranks		70	75	76.5	68	111	84.5
Kruskal-Wallis Rank Sum	P= 0.002	1348	1463	1496	1300	2297	1686
% positive raw residuals	3m(n=119)	66(55)	74(62)	37(31)	69(58)	1(1)	16(13)
	6m(n=87)	49(56)	45(52)	50(57)	43(49)	26(30)	45(52)
	Year 1(n=259)	168(65)	150(58)	202(78)	143(55)	202(78)	215(83)
	Year 2(n=303)	62(20)	62(20)	66(22)	96(32)	218(72)	134(44)
	Year 4(n=336)	186(55)	199(59)	154(46)	224(67)	230(68)	126(38)
	Year 5(n=303)	234(77)	248(82)	222(73)	222(73)	162(53)	167(55)
	Year 7/8(n=314)	152(48)	154(49)	165(52)	86(27)	29(9)	181(58)
	Year 9(n=299)	189(63)	184(62)	202(67)	156(52)	141(47)	237(79)
	Year 10(n=308)	137(44)	125(41)	133(43)	188(61)	245(80)	106(34)

†: Distribution of absolute residuals for each model.

‡: Distribution of absolute residuals for each model at each measurement occasion.

#: Variance components are given with their 95% CI.

***: Medians are given with their Interquartile Range (IQR)**

AIC: - Akaike Information Criterion

BIC: - Bayesian Information Criterion

DISCUSSION

The paper has used mixed effects models to compare the fitness of different infancy and childhood growth models and has demonstrated the benefits of using mixed effects modelling to understand the general patterns of growth in children.

Most previous studies in low- and middle-income countries (LMICs) have used growth centiles to model growth, with an aim to monitor growth and detect timing of growth faltering due to malnutrition by comparing child growth to set growth reference charts (Fetuga et al., 2011, Johnson et al., 2012b, Kalanda et al., 2005b, Maleta et al., 2003a, Mushtaq et al., 2012, Nguyen et al., 2012, Stein et al., 2010) .Of the studies from LMIC that used growth models, none modelled growth beyond 2 years of age and none of them except for the study by Johnson, used mixed effects modelling to fit the growth models (Johnson et al., 2012b, Olusanya and Renner, 2011, Pagezy and Hauspie, 1985, Simondon et al., 1992).

Mixed effects modelling of physical growth measurements allows for the estimation of general population growth pattern as well as that of an individual child and can the incorporation of other factors that can affect child growth in the modelling process (Johnson et al., 2013). Before the advent of mixed effects models, growth curves had to be fitted to each individual child separately (Cameron et al., 1982). And unlike other methods for analysis of longitudinal data such as generalised estimating equations (GEE) and multivariate analysis of variance (MANOVA), mixed effects modelling allows for differences in timings and number of data points per individual (Twisk, 2004, Twisk and de Vente, 2002).

Furthermore, covariance estimates in a mixed effects growth model explain the relationship between starting values and growth trend. There was evidence in the study of SGA exhibiting rapid growth in infancy as shown by the negative covariance estimates. Negative covariance estimates indicate that those with low initial values (e.g. low birth weight) grow faster than those with higher initial values (normal/large babies), while positive covariance indicates that those with initial values below the mean are likely to remain below the mean and those with initial values above the mean maintaining that status (Singer and Willett, 2003, Zimmerman and Nunez-Anton, 2001). Johnson et al, using mixed effects modelling to fit the Berkey-Reed model, also found negative covariance estimates in both Indian and British populations (Johnson et al., 2012a, Johnson et al., 2012b).

Although this study did not show as strong evidence of catch-up growth as the earlier studies by Johnson and colleagues, this could be due to the fact that we are looking at growth from birth to 10 years whereas the earlier studies focussed on the first two years of life when it would be expected that the effect of catch-up growth would be strongest.

In this study, the non-convergence of the models after addition of higher order term could have been due two factors; 1) the limited number of measurement occasions, with long and unequally spaced time intervals, and 2) the lack of variation that is seen in the deceleration of growth across individuals in the early childhood period. Steele (2008), also using mixed effects modelling, showed a significant effect in adding the quadratic term (age^2) to the random component of a 3rd order polynomial model. However, the data used by Steele had 9 equally spaced measurement occasions, between the ages of 11 and 14 years (during

puberty when individual variation in acceleration and deceleration of growth occurs), while the maximum number of data points in this study is 7 spread over 10 year period. Since the addition of the quadratic or ln(age) term in the random component would allow for variations in the period of deceleration in growth amongst the children, the few measurement occasions over a wide age range might have led to computational problems, in that the shape of the growth curve is different from the one being imposed by the model (Simondon et al., 1992). The growth velocity curves (not shown) for the 6 models showed similar period of deceleration in growth. This could be the reason why allowing for variation in deceleration, led to computational problems with this data set and why the results of this study are different to earlier studies.

Even though most of the studies in LMIC that have used the Berkey-Reed 1st order model, have applied it to infant growth data (0-2 years), our study found that it fitted well to the childhood period, compared to the other 5 models (Hauspie and Pagezy, 1989, Johnson et al., 2012b, Pagezy and Hauspie, 1985, Simondon et al., 1992). In study of Indian children, Johnson and colleagues found that the Berkey-Reed 1st order model fitted better to infant weight and height data compared to other models such as the Count and 2nd order polynomial (quadratic) models(Johnson et al., 2012b).

Studies that have modelled weight or height beyond 2 years have used models such as the Jenss-Bayley, Kouchi, adapted Jenss-Bayley and quadratic models, and none of these did a comparative study on the fitness of the different models (Botton et al., 2008, Martin-Gonzalez et al., 2012, van Dommelen et al., 2005, Black and Krishnakumar, 1999, Dwyer et

al., 1983). Some studies have used the quadratic model mainly for its simplicity and not necessarily because the model fits well to the data (Ehrenkranz et al., 1999, Grimm et al., 2011). Biologically, the quadratic model would not be appropriate for the age period under study, as it would not be able to capture the possible acceleration in growth that takes place pre-puberty. Quadratic models have been found to be inappropriate in capturing growth characteristic over longer time intervals (Hauspie et al., 2004).

Although our study found that the Jenss-Bayley model did not fit well in the first year of life, this could be due to the limited number of measurement occasions, leading to the failure by the model to capture the asymptotic nature of the curve in infancy. Further, the limited number of individuals with weight at 3 and 6 months could also have attributed to the failure for the model to fit well at these points. Although the adapted Jenss-Bayley model in general fitted better than the Jenss-Bayley, it also did not fit well in the first year of life. The quadratic term added to the Jenss-Bayley model by Botton et al. , introduced some deceleration effect to minimise the effect of the exponential term (rapid growth) and this possibly helped in capturing the growth in infancy better than if there is just a linear term (Botton et al., 2008). It is worth noting that the study by Botton and colleagues did not compare the goodness of fit of the adapted Jenss-Bayley model with any of the models used in this study. They validated their residual analysis using piece-wise models(Botton et al., 2008).

In general, all of the models seemed to fit to height data better than the weight data, as was evidenced by the non-significant differences in the median values of the absolute residuals.

One of the challenges in modelling weight as opposed to height is that individual weight can fluctuate, and is more sensitive to changes in ecological and environmental factors such as nutrition, while height is monotonic (i.e. increases with age) (Dwyer et al., 1983).

Human growth models are monotonic functions, primarily derived to model monotonic biological processes. Thus ecological and environmental influences that vary those monotonic functions are likely to lead to poorer fitting models, depending on the amount of variation that is driven by biological processes and the amount driven by ecological and environmental influences. Despite this, several studies have shown that the models can fit equally well to weight measurements (Botton et al., 2008, Dwyer et al., 1983, Johnson et al., 2012a, Johnson et al., 2012b, Pagezy and Hauspie, 1985, Simondon et al., 1992, van Dommelen et al., 2005).

LIMITATIONS

The main limitations to this study are the limited data especially during the first 24 postnatal months due to missing data on the growth measurement variables and the number of data collection waves. Having more participants with growth measurements at 3 months and 6 months or more data collection waves (monthly collection) may have helped in improving the fit of the different models to the data, and in picking up the rapid growth in infancy more precisely.

Another factor that could have affected the fit of the models is the time period (birth to 10 years), which might have included the pubertal take-off period, as a study by Jones and colleagues showed that the average age at onset of puberty in this population is around 10

years (Jones et al., 2009). However excluding the measurements at year 10 would have led to a further reduction in the sample size.

Although the number of individuals with a minimum of 5 weight or height measurements was relatively small due to missing data, the distribution of weight and height amongst these individuals with data was not different from that of the other height and weight measurements taken in the cohort.

CONCLUSION

Based on AIC and BIC values, and also the median and maximum of absolute residuals, the best growth model when modelling weight during infancy and childhood (up to ten years) in this South African context, has been shown to be the Berkey-Reed 1st order model.

The Count and the 3rd order Polynomial are also good, as they pick up the rapid growth in infancy, the slowing down in childhood and then the accelerated growth at the beginning of puberty (around 9 years). The other advantage of the Count model is that it has one parameter less than the Berkey-Reed or the 3rd order Polynomial, meaning that fewer data points are required to fit the model. The Adapted Jenss-Bayley model fitted height measurements better than the other models. Also found to fit height data well were the Berkey-Reed 1st order and the Count models.

Overall, the simpler linear Berkey-Reed model seems to fit well to both height and weight for the period from birth to pre-puberty. Simondon et al. , found the Berkey-Reed model fitted best to an African infant growth data (Simondon et al., 1992).

This study extended the findings of Simondon et al to confirm that the model continues to fit well into late childhood (up to 10 years), even though it did not fit well to weight at 3 months, possibly due to limited data at this point, and at 7/8 years due to failure to capture the pre-pubertal growth spurt. A study with shorter intervals between data collection waves in the first 24 months of life would also help in improving the accuracy in fitting the models, since children undergo rapid growth during this period. This study has also demonstrated how mixed effects modelling can be used to compare the fitness of different infancy and childhood growth models.

4.2 SUPPLEMENTARY RESULTS (BT 20 COHORT)

4.2.1 Convergence problems in model fitting to BT 20 cohort

The random components of the mixed effects model were added systematically as outlined in Table 4.5 and the number of iterations before a model converged have also been summarised. Also included are the likelihood ratio values for testing the addition of the term in the random component part of the model.

All models for both weight and height converged and produced standard errors of the random component when random intercept and random slope were added to the fixed component of the model. Convergence problems were encountered in modelling weight when higher order terms which represent deceleration parameters such as ln (age), age^2 were added to the random component of the model. As outlined in the discussion section of 4.1 above, the non-convergence problem for high orders of the random effects might have been due to the inability of the model to find different solutions for individual participants, due to time intervals being far apart, leading to decelerations taking place in same time interval (thus no unique solutions).

Non-linear models (Jenss-Bayley and the Adapted Jenss-Bayley) did not converge as fast as the linear models. Fitting of non-linear models required setting initial values for each of the parameters in the model. Initial values that are far from plausible can affect the speed at which the final solution of the parameters are found and in some instances, failure of the model to find solutions (parameter estimates). Addition of higher order terms than 'age' to the Reed1, Count model, 2^{nd} and 3^{rd} order polynomial led to convergence of the model, and the log-likelihood ratio test was non-significant. Thus, the final random component of each model just included the random intercept and slope.

Table 4.5 Number of iterations and Log-likelihood values for models fitted to the BT 20 cohort.

Model	Function in Random component$^{\beta}$	Weight			Height		
		# of iterations	-2Log L	LR	# of iterations	-2Log L	LR
Reed1	1) intercept	2	12608		2	12210	
	2) age	3	10734		2	11478	732
	3) age, ln(age)	8‡	---		6	11473	5¥
	4) age, ln(age), 1/age	---	---		‡	---	---
Count	1) intercept	2	12872		2	12222	
	2) age	4	11106	1766	2	11488	734
	3) age, ln(age+1)	7‡	---	----	7	11482	6¥
Jenss-Bayley	1) intercept	20	12616		20	14177	
	2) age	18	10731	1885	25	14051	126
	3) age , exp(a + b*age)	‡	---	----	‡	---	---
Adapted Jenss-Bayley	1) intercept	18	13051		21	12700	
	2) age	23	11671	1380	20	12231	469
	3) age, $(age)^2$	‡	---	---	‡	---	---
	4) age, $(age)^2$, exp(a +b*age)	-	---	---	-	---	---
2^{nd} order Polynomial	1) intercept	2	13050		2	12700	
	2) age	12	11670	1380	2	12230	470
	3) age, $(age)^2$	‡	---	---	5	12225	5¥
3^{rd} order Polynomial	1) intercept	2	12620		2	12318	
	2) age	3	10732	1888	2	11662	656
	3) age, $(age)^2$	‡	---	---	4	11656	6¥
	4) age, $(age)^2$, $(age)^3$	---	---	---	‡	---	---

‡: Convergence not achieved; could not estimate the variance components

¥: convergence achieved but Log-likelihood ratio test non-significant.

4.2.2 Model diagnostics for the BT 20 cohort

The residuals from fitting each of the 6 models were tested for normality using normal quartiles plots as shown in Fig 4.3**.** No serious deviations from normality were observed, indicating that the normality assumption of the General Linear model as defined in equation (7) were met. However, the Reed1 and Count models had some positive and negative outliers, as shown by extreme points of the graphs, indicating some lack of fit of the models to the data.

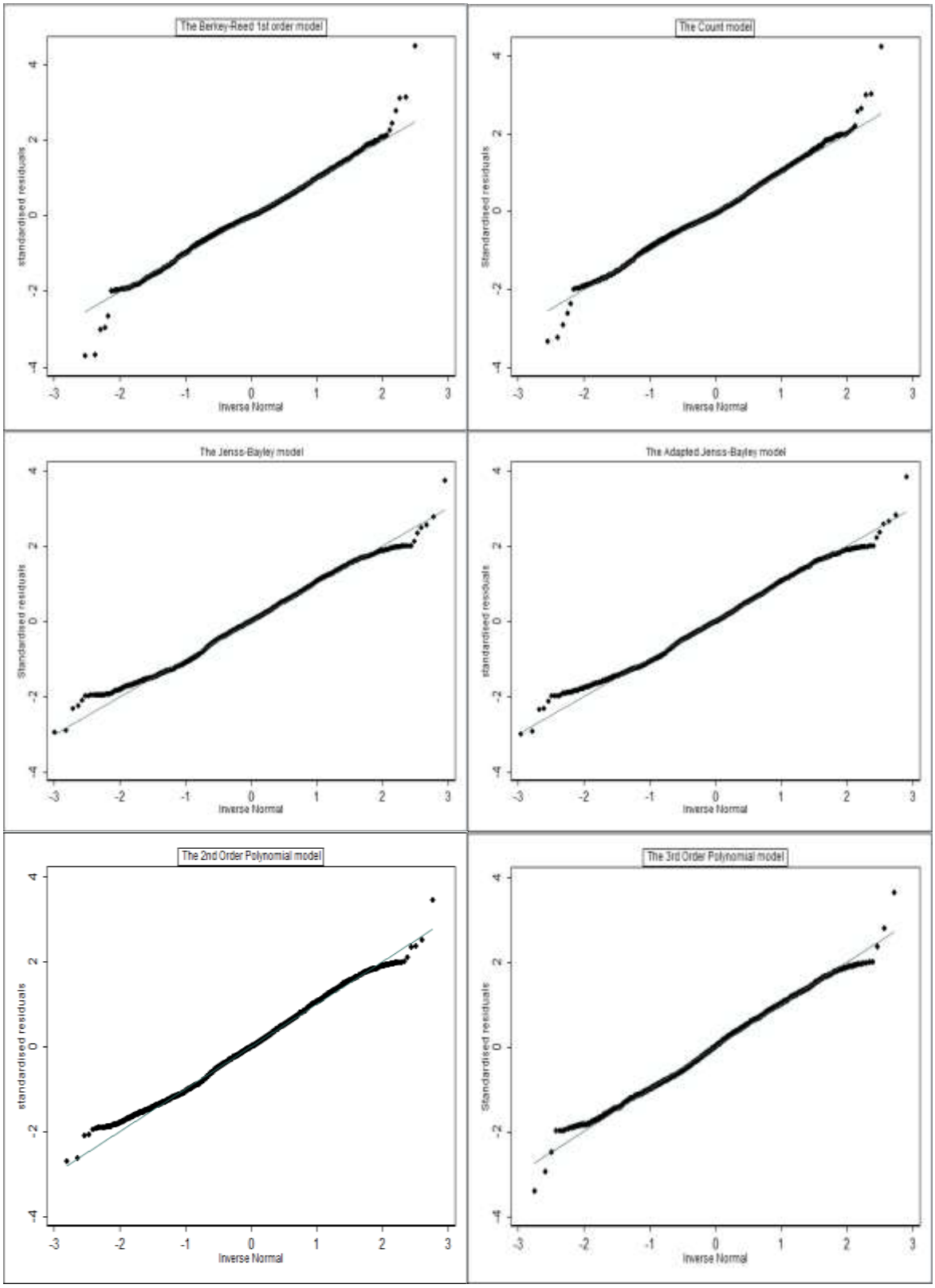


Figure 4.5 Normal quartiles plot of the residuals for weight for BT20 cohort.

4.3 SUPPLEMENTARY RESULTS (LUNGWENA COHORT)

The comparison of the 6 models was also done on the Lungwena cohort to check if the models that fitted well in the BH cohort, also fitted well in this cohort. Results from fitting the growth curve to this cohort have been summarised in Table 4.9 and described later.

4.3.1 Descriptive Statistics

Table 4.6 shows comparison of mean weight and height measurements between the overall Lungwena data set and the "analysis" dataset. The "analysis" dataset consists of all children that met the inclusion criteria outlined in the methodology. There were no significant differences in average weight or height measurements at all the data collection waves between the overall dataset and the "analysis" dataset. Thus, removing participants with few data points and with very high or very low WAZ/HAZ did not affect the general distribution of weight or height at the different data collection waves.

In the "analysis" dataset (Table 4.7), there were significant differences in the average weight between boys and girls from 3 months to 6 years, with boys weighing more than girls (p-value<0.05). From 8 to 10 years, boys still weighed more than girls, but this difference was not significant (p-value>0.05). Similar trends were observed in height, with boys being generally taller than girls from birth to 6 years, but with no significant differences in height from 8 to 10 years.

Table 4.6 Average weight and height in the overall and analysis data sets for Lungwena cohort.

	Overall data set		Analysis data set		
	N	Mean SD	N	Mean SD	sig
Weight					
At birth	548	3.22 ±0.55	359	3.25 ±0.54	0.42
3m	429	5.65± 0.85	291	5.73± 0.81	0.21
6m	416	6.89 ±1.02	301	6.96 ±0.99	0.36
1 yr.	437	8.13± 1.19	324	8.24 ± 1.09	0.19
2 yrs.	413	10.15± 1.38	332	10.28± 1.33	0.19
4 yrs.	403	14.20 ±1.68	342	14.26± 1.63	0.62
5 yrs.	413	15.68± 1.93	354	15.72± 1.89	0.77
6 yrs.	380	16.72± 2.13	318	23.46± 3.00	0.80
8 yrs.	361	23.41± 3.00	318	23.46± 3.00	0.83
10 yrs.	373	25.46 ±3.22	333	25.55 ±3.29	0.81
Height					
At birth	548	48.39± 2.45	359	48.40 ±2.26	0.95
3m	429	56.51± 2.67	291	56.77± 2.59	0.19
6m	416	61.53± 2.78	301	61.58 ±2.76	0.81
1 yr.	437	68.31± 2.95	324	68.49± 2.75	0.39
2 yrs.	413	77.38± 3.72	332	77.60± 3.63	0.42
4 yrs.	403	92.86± 4.47	342	93.11 ±4.45	0.45
5 yrs.	413	99.96± 4.81	354	100.12± 4.70	0.64
6 yrs.	380	106.05 ±6.30	318	106.01± 5.30	0.92
8 yrs.	361	124.28± 5.86	318	124.37± 5.88	0.84
10 yrs.	373	129.26 ±6.26	333	129.26 ±6.18	1.00

NB: No significant differences in mean weight or height observed between the analysis dataset and overall dataset

Table 4.7 Average weight over time for boys and girls in the Lungwena cohort.

	WEIGHT (kg)		HEIGHT(cm)	
	Boys	Girls	Boys	Girls
Birth	3.29 ±0.49	3.21 ±0.59	48.91 ±2.29	47.88 ± 2.12‡
3 m	5.98 ±0.81	5.47 ±0.73‡	57.41± 2.48	56.10± 2.55‡
6 m	7.27 ±1.00	6.66 ±0.87‡	62.51± 2.60	60.62 ± 2.61‡
1 yr.	8.47 ±1.06	7.99 ±1.07‡	69.07 ± 2.74	67.87± 2.63‡
2 yrs.	10.54 ±1.34	10.01 ±1.27‡	78.25 ± 3.76	76.94± 3.38‡
4 yrs.	14.59 ±1.55	13.90 ±1.65‡	93.93 ± 4.34	92.23 ± 4.42‡
5 yrs.	16.01 ±1.79	15.43 ±1.95‡	100.98 ± 4.56	99.24 ± 4.70‡
6yrs	17.12 ±2.09	16.39 ±2.11‡	106.77 ± 5.07	105.23 ± 5.42‡
8 yrs.	23.59 ±2.95	23.33 ±3.04	124.64 ±5.54	124.10 ± 6.20
10 yrs.	25.80 ± 3.14	25.28 ±3.43	129.57± 5.35	128.93 ± 6.93

‡: Significant differences in mean weight or height measurements between boy and girls.

4.3.2 Convergence problems in model fitting

Like in the BH cohort, all models for both weight and height converged and produced standard errors of the random component when random intercept and random slope were added to the fixed component of the model. The Reed model for weight had convergence problems after adding the '1/age' term, while the model height managed to converge even after addition of '1/age' term. However, the addition of this term was not significant. Similarly, the adapted Jenss-Bayley, 2nd and 3rd Order Polynomial model converged after addition of the 'age' term to the weight models. However, the Count and Jenss-Bayley models did not converge after adding terms higher than 'age'.

Models for height seemed to converge faster than when fitted to weight and we were able to add more of the higher order terms in the height models than in the weight models. Non-linear models (Jenss-Bayley and the Adapted Jenss-Bayley) models tended to take longer to converge than the linear models. This could have been due to the initial values used.

Table 4.8 Number of iterations and Log-Likelihood values from models fitted to Lungwena cohort.

Model	Function in Random component$^{\beta}$	Weight			Height		
		# of iterations	-2Log L	LR	# of iterations	-2Log L	LR
Berkey-Reed	1) intercept	2	25670		2	41362	
1st order	2) age	2	22224	3446	2	40064	1298
	3) age, ln(age)	8	21970	254	3	39762	302
	4) age, ln(age), 1/age	11‡	-	-	6¥	39590	172
Count	1) intercept	2	25816		2	39678	
	2) age	2	22462	3354	2	37868	1810
	3) age, ln(age+1)	7‡	-	-	4	37436	432
Jenss-Bayley	1) intercept	14	27413		28	43194	
	2) age	13	24999	2414	33	42252	942
	3)age, exp(a + b*age)	7‡	-	-	27‡	-	-
Adapted	1) intercept	13	27384		11	43017	
Jenss-Bayley	2) age	27	24950	2434	12	42044	973
	3) age, $(age)^2$	36¥	24676	274	27¥	41772	272
	4) age, $(age)^2$, exp(a +b*age)	-	-	-	-	-	-
2nd order	1) intercept	2	27380		2	43016	
Polynomial	2) age	2	24948	2432	2	42044	972
	3) age, $(age)^2$	4	24670	278	4	41770	274
3rd order	1) intercept	2	26282		2	41480	
Polynomial	2) age	2	23294	2988	2	40210	1270
	3) age, $(age)^2$	3	22910	384	3	39742	468
	4) age, $(age)^2$, $(age)^3$	††	-	-	††	-	-

‡: Convergence not achieved
¥: Convergence achieved but LR test non-significant

4.3.3 Fitted models to weight and height measurements

In the Lungwena cohort, estimates for the average baseline weight (intercept), which also represented the estimated birth weight for boys, in the 6 models ranged from 3.06 kg to 5.55kg, with the 2nd order Polynomial model giving the highest estimate (Table 4.9). From the descriptive statistics (Table 4.7), the average birth weight for boys is 3.29 kg. Except for the 3rd order Polynomial and the Jenss-Bayley models, all the other models estimated a linear change in weight of about 200g per month, similar to the estimates in the BH cohort.

The estimates for the effects of sex differences on weight, ranged from -0.44 to -0.47, showing that girls were on average about half a kilogram lighter than boys. The 95% confidence limits ranged from -0.64 to 0.28, indicating that differences in weight between boys and girls range from approximately 300g to 650g. The confidence intervals for the effect of sex in all of the models overlapped, again indicating that there is no significant difference in the estimation of the effect by the 6 models. In all the 6 models, the effect of age and sex interaction was not significant.

In the height models, the estimated average baseline value (intercept), which in the Lungwena cohort represented the estimated average birth length for boys, ranged from 46.98 cm to 61.06 cm, with the Jenss-Bayley model giving the highest estimate and the Count model the lowest. From the descriptive statistics (Table 4.7), the average birth length was 48.91 cm. Estimates for the linear change in height for the 6 models ranged from 4.1 mm to 25 mm per month.

The estimates for the effects of sex differences on height, ranged from -1.46 to -1.54, showing that girls were on average about 1.5 centimetres shorter than boys. The confidence intervals for the effect of sex in all the models overlapped, indicating no significant differences in the estimation of the effect by the 6 models. As in the models for weight measurements, the effect of age and sex interaction in all the 6 models was not significant.

The estimates for the variance component of the weight and height models for the Lungwena cohort are presented in Table 4.10. The estimates for variances (σ^2_{u0}) of the random intercepts (variation in weight at birth) ranged from 0.546 to 0.588, with the 2nd order polynomial model having the smallest estimate. But the confidence intervals for estimates of the random intercept (σ^2_{u0}) for all the models overlapped indicating that there were no significant differences in the estimation of random intercept between the different shapes of curves fitted across the models.

The estimate of the covariance ($\sigma_{u0}\ \sigma_{u1}$) of the random intercept and slope for all the models were all positive, and not significantly different from each other (confidence intervals overlapped). All of the confidence intervals for the covariance estimates included zero, indicating independence between one's initial weight at birth (random intercept) and their growth rates (random slope). All of the models had similar estimates of variance (σ^2_{u1}) of the random slope, with overlapping confidence intervals.

The estimates for variances (σ^2_{u0}) of the random intercepts (variation in birth length) ranged from 4.71 to 5.12, with the 3rd order polynomial model having the smallest estimate. But as in the weight model, the confidence intervals for estimates of the random intercept (σ^2_{u0}) for all the models overlapped indicating that there were no significant differences in the estimation of random intercept between the different shapes of curves fitted across the models.

Similarly, the estimate of the covariance ($\sigma_{u0}\ \sigma_{u1}$) of the random intercept and slope for all the models were all positive, and not significantly different from each other (confidence intervals overlapped) and all of the confidence intervals for the covariance estimates included zero, indicating independence between birth length (random intercept) and their height growth rates (random slope).

Table 4.9 Parameter estimates for the growth models fitted to the Lungwena cohort.

		Weight			Height		
Model	Coefficient	Estimate	Std. Error	95 % Confidence Interval	Estimate	Std. Error	95 % Confidence Interval
Reed1	Intercept	4.92	0.064	(4.80, 5.04)	54.50	0.190	(54.10, 54.90)
	age	0.14	0.002	(0.133, 0.141)	0.471	0.004	(0.463, 0.478)
	Ln(age)	0.72	0.010	(0.699, 0.740)	4.02	0.032	(3.958, 4.084)
	1/age	0.004	0.0002	(0.003, 0.004)	0.023	0.001	(0.022, 0.024)
	Females	-0.47	0.086	(-0.641, -0.302)	-1.539	0.256	(-2.041, -1.037)
	Female*age	-0.003	0.003	(-0.008, 0.003)	-0.0003	0.005	(-0.010, 0.010)
Count	Intercept	3.74	0.071	(3.60, 3.87)	46.98	0.202	(46.59, 47.38)
	Age	0.13	0.002	(0.125, 0.132)	0.409	0.409	(0.402, 0.416)
	Ln(age+1)	1.14	0.016	(1.112, 1.178)	6.845	0.043	(6.760, 6.930)
	Females	-0.46	0.086	(-0.634, -0.294)	-1.504	0.253	(-2.000, -1.008)
	Female*age	-0.003	0.003	(-0.008, 0.002)	-0.0005	0.005	(-0.011, 0.010)
Jenns-Bayley	Intercept	3.06	0.074	(2.93, 3.21)	61.04	0.155	(60.75, 61.35)
	Age	0.46	0.005	(0.455, 0.475)	2.51	0.011	(2.49, 2.52)
	Exp(const)	4.85	0.0005	(4.847, 4.846)	6.32	0.0003	(6.316, 6.320)
	Exp(age)	0.002	2.8e-05	(0.0020, 0.0022)	0.003	1.3e-05	(0.0028, 0.0030)
	Females	-0.46	0.087	(-0.629, -0.287)	-1.48	0.256	(-1.990, -0.984)
	Female*age	-0.003	0.003	(-0.008, 0.002)	0.0002	0.005	(-0.010, 1.416)
Adapted	Intercept	5.56	0.064	(5.43, 5.68)	56.08	0.188	(55.71, 56.45)
Jenss-Bayley	Age	0.20	0.002	(0.195, 0.201)	0.93	0.005	(0.920, 0.939)
	$(Age)^2$	-0.0003	9.2e-06	(-3.5e-04, -3.1e-04)	-0.003	2.7e-05	(-0.0029, -0.0027)
	Exp(const)	-33.00	0.005	-33.01, -32.99)	-33.00	0.004	(-33.01, -32.99)
	Exp(age)	0.15	0.706	(-1.238, 1.538)	0.17	0.509	(-0.835, 1.168)
	Females	-0.47	0.087	(-0.637, -0.295)	-1.46	0.255	(-1.959, -0.956)
	Female*age	-0.002	0.003	(-0.008, 0.002)	0.0002	0.005	(-0.010, 0.117)
2^{nd} Order	Intercept	5.55	0.064	(5.43, 5.68)	56.10	0.188	(55.73, 56.46)
Polynomial	Age)	0.20	0.002	(0.195, 0.203)	0.93	0.005	(0.920, 0.939)
	$(Age)^2$	-0.0003	9.2e-06	(-3.4e-04, -3.1e-04)	-0.003	0.00003	(-0.0029, -0.0027)
	Females	-0.46	0.087	(-0.632, -0.291)	-1.49	0.255	(1.988, -0.988)
	Female*age	-0.003	0.003	(-0.008, 0.002)	0.0002	0.005	(-0.010, 0.010)
3^{rd} Order	Intercept	4.73	0.066	(4.60, 4.85)	53.54	0.195	(53.16, 53.92)
Polynomial	Age	0.30	0.003	(0.296, 0.308)	1.25	0.008	(1.236, 1.262)
	$(Age)^2$	-0.003	5.7e-05	(-0.0027, -0.0026)	-0.01	0.0002	(-0.011, -0.010)
	$(Age)^3$	0.00001	3.2e-6	(1.3e-05, 1.4e-05)	0.00004	9.3e-07	(4.04e-5, 4.4e-05)
	Females	-0.45	0.086	(-0.623, -0.283)	-1.47	0.256	(-1.967, -0.964)
	Female*age	-0.003	0.003	(-0.008, 0.003)	-0.001	0.005	(-.011, 0.009)

Table 4.10 Variance component estimates for models fitted to the Lungwena cohort.

Model	Variance Component	Weight model	Height model
Reed1	Random Intercept	0.578 (0.488, 0.684)	5.01 (4.21, 5.95)
	Random Slope	0.0006 (0.0004, 0.0007)	0.002 (0.001, 0.0024)
	Covariance	0.0004 (-0.0016, 0.0025)	0.015 (0.002, 0.026)
	Random Residuals	0.718 (0.695, 0.741)	6.90 (6.68, 7.13)
Count	Random Intercept	0.578 (0.488, 0.685)	5.09 (4.32, 6.01)
	Random Slope	0.0006 (0.0004, 0.0007)	0.002 (0.001, 0.0024)
	Covariance	0.0004 (-0.002, 0.002)	0.013 (0.001, 0.025)
	Random Residuals	0.741 (0.717, 0.765)	5.12 (4.95, 5.28)
Jenss-Bayley	Random Intercept	0.588 (0.490, 0.687)	5.12 (4.30, 5.98)
	Random Slope	0.0006 (0.0004, 0.0007)	0.002 (0.001, 0.002)
	Covariance	0.0009 (-0.001, 0.003)	0.015 (0.002, 0.027)
	Random Residuals	1.05 (1.02, 1.08)	9.29 (8.99, 9.59)
Adapted Jenss-Bayley	Random Intercept	0.579 (0.489, 0.679)	5.00 (4.20, 5.94)
	Random Slope	0.0005 (0.0004, 0.0006)	0.002 (0.001, 0.002)
	Covariance	0.0009 (-0.001, 0.003)	0.015 (0.002, 0.027)
	Random Residuals	1.04 (1.02, 1.07)	9.02 (8.73, 9.31)
2^{nd} order Polynomial	Random Intercept	0.546 (0.456, 0.654)	5.00 (4.20, 5.94)
	Random Slope	0.0005 (0.00045, 0.0006)	0.002 (0.001, 0.002)
	Covariance	0.0011 (-0.001, 0.003)	0.015 (0.002, 0.027)
	Random Residuals	1.04 (1.01, 1.08)	7.03 (6.81, 7.26)
3^{rd} Order Polynomial	Random Intercept	0.570 (0.479, 0.677)	4.71 (3.92, 5.65)
	Random Slope	0.0005 (0.0004, 0.0006)	0.002 (0.001, 0.003)
	Covariance	0.0008 (-0.001, 0.003)	0.019 (0.007, 0.032)
	Random Residuals	0.831 (0.805, 0.858)	9.03 (8.74, 9.33)

4.3.4 Goodness of fit statistics for the weight and height models

The Reed1 model had the smallest AIC, BIC, random residual and smallest 'maximum residual' values amongst all the 6 models of weight and second smallest AIC, BIC and random residual variance values for the height model (Table 4.11). Overall the Reed1 model had the smallest rank sum value for both weight and height models. Thus, the Reed1 model was found to fit well to both weight and height measurements.

Table 4.11 Goodness of fit statistics for the 6 models fitted to the Lungwena cohort

	Residual variance	AIC	BIC	Median absolute residuals	Max absolute residuals	Rank sum‡	p-value
Weight							
Reed1	0.72 (0.70, 0.74)	22244	22314	0.540	5.067	20	
Count	0.74 (0.72, 0.77)	22481	22544	0.545	5.913	70	
Jenss-Bayley	1.05 (1.02, 1.08)	25019	25058	0.542	5.156	110	
Adapted Jenss-Bayley	1.04 (1.02, 1.07)	24973	25015	0.541	5.179	85	
2nd order Polynomial	1.04 (1.01, 1.08)	24967	25030	0.530	5.875	85	
3rd order Polynomial	0.83 (0.80, 0.86)	23315	23385	0.573	6.082	95	0.029
Height							
Reed1	6.90 (6.68, 7.12)	40085	40155	0.515	4.489	30	
Count	5.12 (4.95, 5.29)	37887	37950	0.564	4.826	45	
Jenss-Bayley	9.29 (8.99, 9.59)	42273	42312	1.563	13.714	125	
Adapted Jenss-Bayley	9.02 (8.73, 9.31)	42067	42110	1.548	13.487	110	
2nd order Polynomial	9.03 (8.74, 9.32)	42063	42126	0.551	4.547	85	
3rd order Polynomial	7.03 (6.81, 7.26)	40230	40300	0.584	4.505	70	0.003

‡ The value of each statistic was ranked across the 6 models and the ranks for the models were then compared using Kruskal-Wallis test

4.3.5 Model diagnostics

Plots of the standardised residuals from fitting the 6 models to weight measurements showed random variation of the residuals over time (Figure 4.4). The Normal plot also showed the residuals were normally distributed, thus meeting the assumption of the General Linear model.

However, there were a number of very large residuals (|r|>2) that were picked up by all the 6 models.

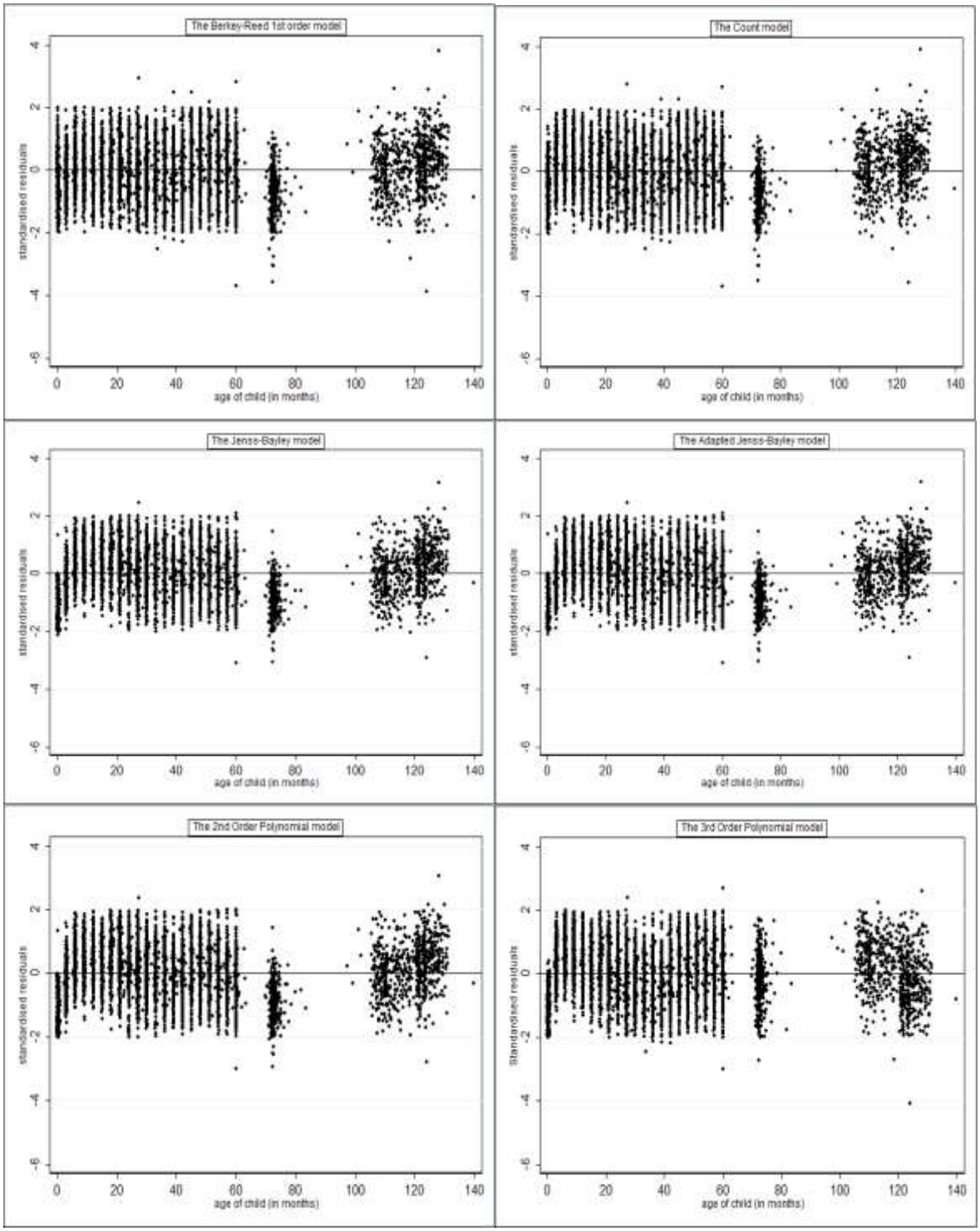


Figure 4.6 Standardised residuals for weight measurements of the Lungwena cohort.

4.4 WORKFLOW FOR MULTILEVEL MODELLING OF GROWTH DATA.

Below is a summary of the steps to consider when modelling child growth data.

1. Choose appropriate growth models to be considered based on knowledge of the biology of growth and aided by graphical representation of growth measurements over time.

2. Determine the minimum number of data points for each participant that is required to fit model with largest number of parameters.

3. Check for the appropriateness of different covariance structure.

4. Identify appropriate covariates to be included in the model and how they will be modelled (fixed effects, random effects or as interactions).

5. Starting with the simplest form of each model (model with random intercept only), use stepwise regression approach to add higher order functions of age and other covariates to the random component of the multilevel model. At each addition, statistical tests should be done to check for the significance of the addition by looking at the change in deviance (likelihood values). The models should also be checked for convergence.

6. When addition of further higher order terms is no longer significant, the best fitting curve should be determined using various fit statistics (likelihood values, Akaike Information Criterion (AIC), differences between observed and predicted measurements and residual standard deviations).

7. Check for any correlation between size of the deviations of the predicted measurements from the observed and the different periods of time over which model has been fit (e.g infancy, early childhood, late childhood).

8. Assess the general linear model assumptions of normality of level 1 residuals.

CHAPTER 5: MISSING DATA IN PHYSICAL GROWTH MEASUREMENTS

This chapter deals with missing data challenges in the modelling of the physical growth measurements in the two cohorts. The chapter presents results from using different statistical methods of dealing with intermittent missing data in longitudinal studies. The chapter consists of a paper publication submitted to the BMC Medical Research Methodology (Section 5.1), which was based on simulated missing growth measurements, as outlined in Figure 3.2 of the study methodology, and results based on actual missing data (Section 5.2) as outlined in Figure 3.3 of the study methodology.

5.1 PAPER 2

Title: Intermittent missing measurements in longitudinal study of physical growth of children: Is it necessary to impute?

Journal submitted to: BMC Medical Research Methodology

INTRODUCTION

One of the main challenges in the analysis of data from studies that involve repeated measurements over time such as growth monitoring studies is the inevitability of missing information. Missing data in studies of physical growth can arise due to participants being lost to follow up due to migration, dropping out or missing scheduled visits. Ignoring individuals with missing data in the analysis of such longitudinal studies by using a complete case analysis (CCA) can lead to biased results, especially if the individuals with missing data have different characteristics to those with complete data. In longitudinal studies, CCA can also lead to a substantially reduced sample size, especially where there are a large number of data waves, thus leading to loss of power (Blankers et al., 2010, Engels and Diehr, 2003).

Researchers have used different methods to deal with missing data in longitudinal studies and these include imputing the missing information, analysing ignoring individuals with missing information or analysing the data using the available partial information. Whether to impute or not, and which imputation method to use, depends on the reason for analysis, the type of variable, the amount of missing data and the pattern of missing data (intermittent or monotonic) (Mallinckrodt et al., 2003, Sterne et al., 2009).

The risk of bias in estimates and the magnitude of the effect due to CCA depends on the mechanism behind the missing data patterns as defined by Little and Rubin (Little and Rubin, 2002, Mallinckrodt et al., 2003, Sterne et al., 2009). Under missing completely at random (MCAR) and missing at random (MAR), ignoring cases with missing data can still produce valid results. The major concern would be the reduced sample size which can lead to loss of power. However, if data are missing not at random (MNAR), ignoring cases with missing data

would lead to biased estimates and, thus, affect the validity of the findings (Blankers et al., 2010, Twisk and de Vente, 2002). Further, it is usually difficult to distinguish between MAR and MNAR since MNAR depends on unobserved data (Grittner et al., 2011, Sterne et al., 2009).

Researchers have used different methods to impute for missing data in longitudinal studies. These methods range from ones that use population group information to those that use the longitudinal nature of the data in each case, such as Last Observation Carried Forward (LOCF), and linear interpolation (Engels and Diehr, 2003, Grittner et al., 2011, Tang et al., 2005, Twisk and de Vente, 2002). Although studies have shown that in general, methods that use the longitudinal nature of the data such as linear interpolation to impute values are better than cross-sectional population based methods, applying them to physical growth data in children might not be appropriate (Engels and Diehr, 2003, Grittner et al., 2011, Twisk and de Vente, 2002). Physical growth in children is characterised by rapid non-linear growth, especially in infancy, thus applying linear interpolation to impute for missing growth measurements might produce values that either grossly underestimate or overestimate the measurements.

With advances in statistical software, Multiple Imputation (MI) has become one of the more common methods used in dealing with bias due to loss of information from missing data. MI allows for uncertainty about the missing data by creating a number of datasets in which all missing values are replaced by the imputed values calculated based on some posterior distribution (Engels and Diehr, 2003, Spratt et al., 2010). While MI can help in reducing bias, Carpenter et al cautions against its indiscriminate use (Carpenter et al., 2007). They argue that

MI, which is based on MAR assumption, can bring in some bias if the imputation model is wrongly defined. Under MAR, the probability of missing values is related to some observed variables. Thus, it is important to identify any factors associated with the outcome and to include such factors in the imputation model (He et al., 2011, Kenward and Carpenter, 2007, Sterne et al., 2009). In child physical growth modelling, these factors may include maternal and household characteristics that are known to affect child growth. Apart from inclusion of the factors that affect growth in the imputation process, MI may also be affected by the amount of information already available, i.e. the number of data points per participant (Graham, 2009).

Advances in statistical methods have also enabled researchers to use the available information in a data set to measure effects rather than excluding cases where any data are missing. The Available Case Analysis (ACA) methods include Linear mixed effects (LME) regression and generalised estimating equations (GEE). LME has been used in modelling growth, since apart from the flexibility of including a random component to describe the variations in individual growth profiles, the methods may be used to fit structural (parametric) and non-structural (non-parametric) curves. The superiority of ACA methods over CCA is due to the fact that ACA methods incorporate the partial information from cases with missing data. However, the methods can also lead to biased results if missing data are not MAR. The performance of the LME model will also depend on the amount of missing observations per participant (Blankers et al., 2010, Peters et al., 2012).

This study assessed whether in growth modelling it is necessary to impute for missing physical growth measurements from infancy to late childhood and examined how the time interval between data collection waves affects the performance of the different methods of dealing with

missing data in longitudinal growth monitoring studies. This study built upon work by Peters et al. (2010) which used linear mixed effects modelling to compare ACA and MI with CCA using longitudinal measurements to assess the added value of performing MI in dealing with missing data in repeated outcome measures of a longitudinal dataset. While the study by Peters et al looked at the effect of changing the percentage of missing data, our study looked at whether data collection wave intensity affects the performance of the different methods of dealing with longitudinal missing data. While most studies use linear interpolation, this study used growth model-based interpolation.

METHODS

The methods used for the paper have been outlined in section 3.2.2.2 and in Figure 3.2

RESULTS

Descriptive Analysis

There were no significant differences in maternal, household and child characteristics, such as sex of the child, birth-weight, maternal height, maternal age and SES-level, between complete and incomplete cases for both cohorts ($0.10 < p\text{-value} < 0.78$, Table 5.1). Growth profiles of a random selection of children from the BH and LCSS studies (Fig 5.1), in general showed interpolated values being closer to observed values than most multiple imputed values.

Table 5.1 Characteristics of children with complete or with missing weight and height measurements.

		Complete	With missing data	p-value
a) BH Study				
Child Characteristics				
i) Sex	Boys	54 (60)	160 (50)	
	Girls	36 (40)	160 (50)	0.10
ii) Parity	1	42 (46.7)	109 (41.6)	
	2	22 (24.4)	79 (30.2)	
	>=3	26 (28.9)	74 (28.2)	0.56
iii) SGA	No	84 (93.3)	242 (92.4)	
	Yes	6(6.7)	20(7.6)	0.76
iv) Birth weight (kg)	Mean(sd)‡	3.2(0.42)	3.1(0.52)	0.13
v) Gestation age (weeks)	Mean(sd)‡	38.2(0.96)	38.4(1.11)	0.12
Maternal Characteristics				
i) Education	< Std 5	9 (10)	42 (13.5)	
	Std 6-8	47 (52.2)	131 (42)	
	Std 9-10	28 (31.1)	108 (34.6)	
	>= Std 10	6 (6.7)	31 (9.9)	0.34
ii) Height (cm)	Mean(sd)‡	156.8 (8.2)	158.0(6.4)	0.17
iii) Age at birth of child (yrs.)	Mean(sd)‡	25.1(6.06)	25.3 (6)	0.78
b) LCCS Study				
Child characteristics				
i) Sex	Boys	78 (56)	208 (51)	
	Girls	62(44)	200(49)	0.38
ii) SGA	No	132(94.3)	374 (91.7)	
	Yes	8(5.7)	34(8.3)	0.36
iii) Birth weight (kg)	Mean (sd)‡	3.2 (0.46)	3.2 (0.57)	0.71
iv) Gestation age (weeks)	Mean (sd)‡	40.5 (2.3)	40.3 (2.30)	0.38
Household Characteristics				
SES- level	Low	58 (41.4)	159 (40.8)	
	Middle	51 (36.4)	156 (40.0)	
	High	31 (22.2)	75 (19.2)	0.68

‡: All characteristics are summarised using frequency with percentages in parentheses, except for birth weight, maternal height and age, and gestation age, which are represented by means and standard deviations. Proportion test was used to compare the percentages and t-test was used to compare the means.

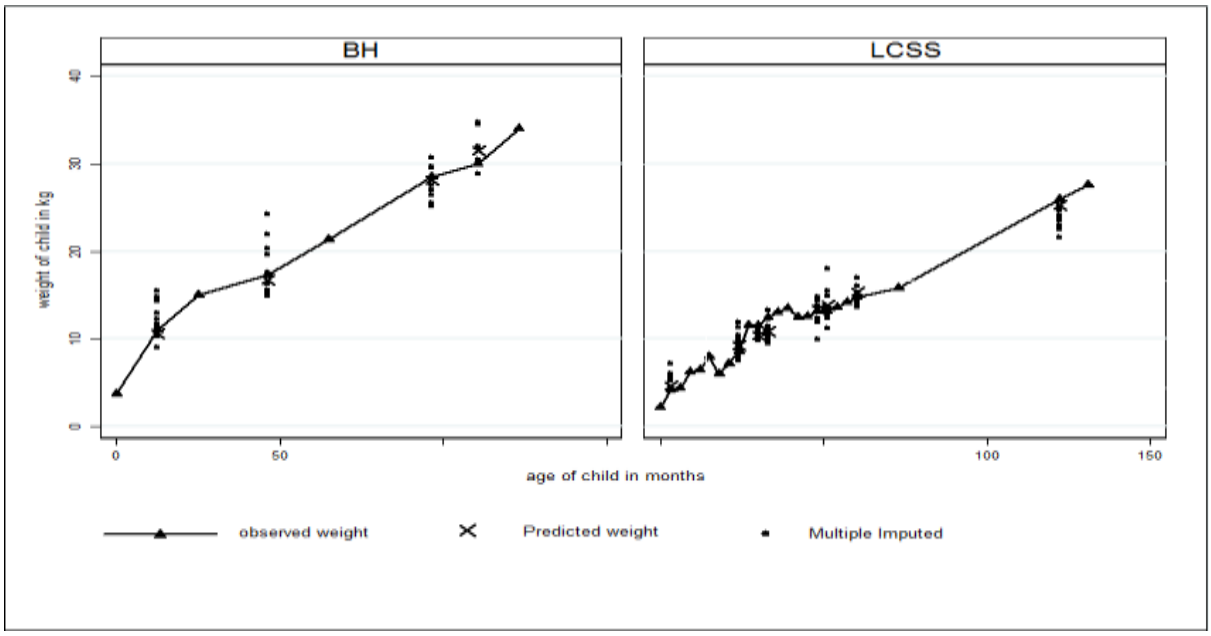


Figure 5.1 Profile plot of 2 randomly selected children from the 2 cohorts.

Modelling data from BH study

In modelling weight using data from the BH study, Multiple Imputation (MI) produced parameter estimates that were on average slightly more biased than those derived from using regression imputations (RI) or the ACA method. The average RBIAS values for the MI were in general higher than those derived using ACA or interpolation (Table 5.2). There were no significant differences in the RBIAS of parameters between ACA and RI. Of the 50 estimates of the intercepts (Bo) derived using MI, about 10 % were outside the 95% confidence limits of the intercept derived using the original complete data. All parameter estimates derived using ACA or RI were within the 95% confidence limits of the CCA parameters.

Consistent with results from the model for weight, parameter estimates from RI for the height models were largely similar to the ACA parameter estimates, with average RBIAS values from RI similar to those from the ACA method.

However, standard errors for parameter estimates from the regression imputation method were consistently smaller than those from ACA. This is expected since regression imputed values used were predicted from fitting model to data with missing values (ACA method), thus reducing the variation in the measurements. The reduction in the variation due to RI method was also shown by the overall mean square errors (MSE) after fitting the models (Table 5.4). In both weight and height models, the MSE values for the RI analysis were consistently smaller than those from the ACA method or MI method. Consistent with the RBIAS values, the root of the relative mean square error (RRMSE) also showed no significant differences in the estimates of the MSE between the ACA and RI methods. The large variation in the MI values for the weight models were also shown by the larger MSE values from the MI method relative to the other methods, giving RRMSE values that were greater than 1.

There is relatively more bias in the estimation of the coefficients of the '***1/age'*** and '***ln (age')'*** terms of both weight and height models, indicating a general instability in the estimation of these parameters by all the methods. The height models also produced high RBIAS values for the estimate of the constant term (Bo), indicating increased variation in the estimation of the initial individual height values of the children. This could be due to the model for height starting at 1 year when measurements are more variable, rather than at birth as is the case with the model for weight. Even though there were some biases in the parameter estimates of the 3 methods, paired t-tests showed no significant differences between observed, predicted, or average of multiple imputed measurements (Table 5.5).

Table 5.2 Average relative bias in parameter estimates for weight models with simulated missing data.

		AVAILABLE CASE ANALYSIS		REGRESSION IMPUTATION		MULTIPLE IMPUTATION	
	Parameter	Mean RBIAS (sd)	% coverage	Mean RBIAS (sd)	% coverage	Mean RBIAS (sd)	% coverage
BH study^{boys}	B_0	2.32 (2.15)	100	2.32 (2.15)	100	2.58 (2.02)	92.5
	B_1 [age]	0.88 (1.15)	100	1.01(1.03)	100	0.99 (0.93)	100
	B_2 [lnage]	5.78 (5.08)	100	5.78 (5.08)	100	5.97 (4.91)	100
	B_3 [1/age]	4.16 (5.41)	100	4.17 (5.41)	100	5.00 (4.93)	100
BH study^{girls}	B_0	2.36 (1.40)	100	2.36 (1.40)	100	3.17 (1.96)	90
	B_1 [age]	0.91 (0.77)	100	0.97 (0.69)	100	0.84 (0.72)	100
	B_2 [lnage]	4.68 (3.16)	100	4.69 (3.17)	100	5.87 (3.21)	97.5
	B_3 [1/age]	4.78 (3.52)	100	4.78 (3.52)	100	5.11 (3.09)	100
LN study^{boys}	B_0	0.15 (0.12)	100	0.15 (0.12)	100	0.26 (0.23)	100
	B_1 [age]	0.26 (0.34)	100	0.26 (0.34)	100	0.61 (0.48)	100
	B_2 [lnage]	0.69 (0.49)	100	0.68 (0.45)	100	3.51 (1.07)	100
	B_3 [1/age]	0.01 (0.02)	100	0.01 (0.02)	100	1.68 (1.18)	100
LN study^{girls}	B_0	0.25 (0.18)	100	0.26 (0.19)	100	0.78 (0.33)	100
	B_1 [age]	0.30 (0.35)	100	0.28 (0.35)	100	0.47 (0.52)	100
	B_2 [lnage]	0.71 (0.64)	100	0.71 (0.64)	100	2.04 (1.39)	100
	B_3 [1/age]	0.01 (0.02)	100	0.01 (0.02)	100	0.83 (5.26)	100

Mean RBIAS (sd): Average and standard deviation of the relative bias calculated from the 50 datasets.
RBIAS : Calculated relative to parameter estimates from Complete Case Analysis.
% coverage: Calculated as the percentage of the number of times the estimated parameter was within the 95 % confidence interval of its corresponding parameter derived from Complete Case Analysis.

Table 5.3: Average relative bias in the parameter estimates of height models with simulated missing.

		AVAILABLE CASE ANALYSIS		INTERPOLATION		MULTIPLE IMPUTATION	
	Parameter	Mean RBIAS (sd)	% coverage	Mean RBIAS (sd)	% coverage	Mean RBIAS (sd)	% coverage
BH study^{boys}	B_0	8.08 (5.06)	100	7.88 (4.76)	100	8.22 (5.15)	100
	B_1 [age]	2.62 (1.97)	100	2.54 (1.85)	100	2.62 (1.97)	97.5
	B_2 [lnage]	4.07 (2.66)	92.5	3.95 (2.51)	97.2	4.07 (2.66)	92.5
	B_3 [1/age]	46.5 (29.8)	97.5	45.2 (28.1)	100	46.5 (29.8)	92.5
BH study^{girls}	B_0	18.8 (7.47)	100	18.8 (7.75)	100	18.8 (7.47)	100
	B_1 [age]	4.60 (1.64)	100	4.57 (1.72)	100	4.60 (1.63)	100
	B_2 [lnage]	13.3 (5.04)	100	13.2 (5.26)	100	13.3 (5.04)	100
	B_3 [1/age]	43.6 (18.9)	100	43.2 (19.5)	100	43.6 (18.9)	100
LN study^{boys}	B_0	0.55 (0.08)	100	0.54 (0.10)	100	0.53 (0.09)	100
	B_1 [age]	0.17 (0.14)	100	0.18 (0.13)	100	0.24 (0.21)	100
	B_2 [lnage]	2.02 (0.30)	100	2.01 (0.36)	97.5	3.50 (0.49)	87.5
	B_3 [1/age]	0.21 (0.93)	100	0.21 (0.93)	100	4.50 (1.72)	87.5
LN study^{girls}	B_0	0.52 (0.08)	100	0.52 (0.11)	100	0.72 (0.11)	100
	B_1 [age]	0.12 (0.12)	100	0.12 (0.12)	100	0.35 (0.28)	100
	B_2 [lnage]	2.02 (0.29)	100	2.02 (0.34)	100	1.53 (0.69)	100
	B_3 [1/age]	3.94 (1.51)	100	3.82 (1.63)	100	4.50 (1.03)	100

Mean RBIAS (sd): Average and standard deviation of the relative bias calculated from the 50 datasets.
RBIAS : Calculated relative to parameter estimates from Complete Case Analysis.
% coverage: Calculated as the percentage of the number of times the estimated parameter was within the 95 % confidence interval of its corresponding parameter derived from Complete Case Analysis.

Modelling data from LCSS Study

Consistent with BH study results, there were no significant differences in the parameter estimates from the CCA, ACA, MI and RI methods when the Berkey-Reed model was fitted to the Lungwena cohort for both height and weight measurements. All the average RBIAS values of the parameter estimates for the weight and height models were less than 5% (Table 5.2 & 5.3). Unlike in the BH study, there was less bias in the coefficients of '1/age' of the weight models for all the 3 methods. However the results for the height models are consistent to what was observed in the BH study, with the average RBIAS values for the coefficient of '1/age' higher than those of the other coefficients of the model.

The non-significant differences in the model estimates amongst the methods was also evidenced by the lack of significant difference in the observed, predicted and multiple imputed mean values in this cohort (Table 5.5).

Similarly, there were no differences in the average RRMSE values indicating no differences in the residual variations from fitting the model using the 3 methods. Almost all estimated parameters were within the 95 % confidence limits of their corresponding CCA parameters. In general, there was reduced bias in the parameter estimates in the LCCS study compared to the BH study for both weight and height models.

Table 5.4 The average RRMSE for models fitted to weight and height measurements.

		ACA	REGRESSION IMPUTATION	MULTIPLE IMPUTATION
		Mean RRMSE (sd)	Mean RRMSE (sd)	Mean RRMSE (sd)
Weight	BH ^{boys}	1.01 (0.02)	0.92 (0.01)	1.03 (0.02)
	BH ^{girls}	1.00 (0.02)	0.91 (0.01)	1.05 (0.04)
	LCCS ^{boys}	1.00 (0.01)	0.90 (0.01)	0.96 (0.01)
	LCCS ^{girls}	1.00 (0.01)	0.90 (0.01)	0.96 (0.01)
Height	BH ^{boys}	0.97 (0.03)	0.90 (0.04)	0.95 (0.04)
	BH ^{girls}	0.99 (0.03)	0.90 (0.02)	0.97 (0.03)
	LCCS ^{boys}	1.01 (0.01)	0.91 (0.01)	0.94 (0.01)
	LCCS ^{girls}	1.02 (0.01)	0.91 (0.01)	0.95 (0.01)

Mean RRMSE (sd)‡: Average and standard deviation of the RRMSEs calculated from the 50 datasets.
RRMSE : Calculated relative to MSE from Complete Case Analysis.

Table 5.5 Mean comparison of observed, predicted and multiple imputed measurements

		<= 48 months			>48 months		
		n	Mean diff (sd)	sig	n	Mean diff (sd)	sig
WEIGHT							
BH Study	Obs vs RI	360	-0.03 (0.54)	0.22	360	-0.06(0.52)	0.09
	Obs vs MI	360	0.01(0.72)	0.89	360	-0.06(0.77)	0.14
	RI vs MI	360	0.04(0.70)	0.28	360	0.001(0.59)	0.96
LCCS Study	Obs vs RI	2380	0.01(0.32)	0.23	980	-0.03(0.48)	0.11
	Obs vs MI	2380	0.01(0.41)	0.14	980	-0.02(0.52)	0.13
	RI vs MI	2380	0.004(0.25)	0.40	980	0.01(0.39)	0.68
HEIGHT							
BH Study	Obs vs RI	270	-0.04(1.01)	0.37	360	-0.04(0.91)	0.29
	Obs vs MI	270	-0.04(1.30)	0.55	360	-0.05(1.03)	0.35
	RI vs MI	270	0.01(0.76)	0.87	360	-0.001(0.43)	0.98
LCCS Study	Obs vs RI	2380	-0.05(0.99)	0.12	980	0.21(1.02)	0.24
	Obs vs MI	2380	-0.05(1.13)	0.21	980	0.21(1.19)	0.35
	RI vs MI	2380	0.001(0.51)	0.91	980	-0.01(0.68)	0.73

- RI:- Predicted measurements MI:- Multiple Imputed measurements Obs:- Observed measurements
- Paired t-test used to compare predicted, multiple imputed and observed measurements weight and height measurements.

DISCUSSION

This paper has examined the consequences of missing data on the parameter estimates of physical growth models for African children. This was done by comparing estimates of the Berkey-Reed model fitted to datasets without missing data (CCA), to datasets with missing data (ACA) and to datasets in which the missing data were imputed by different imputation methods (RI and MI). These African datasets came from 2 different longitudinal studies, which had different intensity of data collection waves, but same period of time (birth to 10 years).

Consistent with results from Peters et al. (2012), our study found no added values in using MI over ACA, nor did we find significant change in parameter estimates between regression imputation and ACA, apart from increasing the number of observations. While the study by Peters et al. (2012) examined the performance of the different methods under varying degrees of missing data, our study did not vary the percentage of missing data. However, we looked at how the intensity in the data collection waves would affect the performance of the different methods. The BH study, which had a maximum of 8 data points per individual between birth and 10 years, exhibited more instability in the estimation of model parameters than the LCCS study. The latter had 24 data points per individual, but within same age period as the BH study.

The instability in the estimation of the model parameter was shown by large biases in estimates in the Bone Health cohort compared to the Lungwena cohort for both weight and height models and was more pronounced in the estimation of the deceleration terms of the model. The differences in the magnitude of the mean RBIAS between BH study and LCCS study for both weight and height models is thus, evidence of the effect of time interval and number of data points on the performance of the different methods of dealing with missing data in studies of

child growth. In the Lungwena cohort, where data in the infancy are at 3 months intervals, the gaps created by missing values would not be as large as those created in the Bone Health cohort, where measurement intervals were a year or more apart. The instability due to effect of number of data points was not specific to a particular method, as all methods had similar mean RBIAS values.

However, the large gaps created in the BH study led in some instances to model convergence problems when using ACA methods. The non-convergence may have been due the level of 'unbalancedness' in the data created by the missing information. Even though LME modelling allows for unbalanced data (differences in data collection waves), its performance can be affected by the amount of unbalancedness in the data (Singer and Willett, 2003). No convergence problems were encountered in modelling the LCCS data, or when using MI or predicted values with the BH study data. This could point to some benefit in using MI in dealing missing data, when there are large time intervals between data collection waves.

Care must be taken in defining an appropriate imputation model that will take into account an individual child's growth trajectory in the imputation process. Failure to define an appropriate imputation model can lead to biased imputation. In our study we found that not including the clustering variable in the imputation model, which would take account of a child's individual growth trajectory in the imputation process, produced large variations in the imputed values, leading to very large standard errors and large biases in the parameter estimates. Even though multiple imputation incorporates information from subjects with incomplete sets of observations in its modelling process and allows for more covariates to be used in the imputation model than in the analysis model to reduce bias and increase precision, the efficiency and reduction in bias depends on how good the imputation and substantive analysis models are (Carpenter et al., 2007, Daniels and Hogan, 2008, Engels and Diehr, 2003, Grittner

et al., 2011, He et al., 2011). Although a number of studies have shown that multiple imputation is suitable in many longitudinal settings with missing values, our study highlighted the need to be cautious in the application of MI, by taking into consideration the type of data used (Graham, 2009, Spratt et al., 2010, Tang et al., 2005, Twisk and de Vente, 2002). Peters et al also highlighted reasons why MI might not offer any advantage over LME modelling in repeated outcome measurements (Peters et al., 2012). They explain that LME and MI are expected to give similar results if the imputation model is similar to the LME model. For child growth data, the correlation between successive measurements is important in the imputation of missing values. Ignoring the collinearity of observations in the imputation process can lead to imprecise imputations.

Although the results indicate that it is not really necessary to use predicted values if the objective is to describe growth, the non-significant difference from the regression imputation analysis relative to ACA and CCA indicate that regression imputations can give good predicted values for the missing measurements. This was also shown by the non-significant difference in observed and predicted measurements. This can help in the prevention of loss of power due to reduced number of observations (missing values). The main advantage of mixed model regression imputation is that it uses individual child growth profiles to impute the missing values. Regression imputations using a defined growth curve takes into account the rate of growth in the imputation process apart from the age difference between any 2 observed measurements since the growth curve used is a function of age. However, the performance of the method will depend on how well the growth curve fits to the child's growth trajectory. Several studies have used different regression models with physical growth data (He et al., 2011, Kamal et al., 2011, Lee et al., 2012, Yasubayashi et al., 2012). The objectives for these have ranged from predicting measurements in between scheduled visits so as to increase

information used in defining age estimates for growth velocity rather than to estimate missing growth data due to missed scheduled visits, to comparing rural and urban children (Fujii et al., 2012, Lee et al., 2012). Unlike our study, these studies did not use Linear Mixed Effects (LME) modelling, which allows for missing data, to fit the growth curves and excluded any participant with missing data.

CONCLUSIONS

In conclusion, this study found no significant differences in the model parameter estimates between complete data, incomplete data, regression imputed data and multiple imputed data, indicating no significant gain in model precision whether by MI or mixed model RI relative to ACA approach. However, MI helped in dealing with convergence problems due to unbalanced data, created by missing information when time interval between data points is large. In terms of simplicity of analysis, regression imputation is easier to use than MI.

5.2 SUPPLEMENTARY RESULTS

This section outlines results from comparing the different methods of dealing with missing data, using datasets with actual missing measurements as outlined in Figure 3.3 in Section 3.2.2.2.

5.2.1 Modelling using the BH cohort

In comparing imputation methods using actual missing data, the bias in the parameter estimates from RI and MI were calculated relative to the ACA method (Table 5.6). There were no significant differences in the parameter estimates between the RI method and ACA method in both weight and height models (RBIAS values<2 %). However there was some bias in the estimation of the coefficient of ***'ln (age)'*** and ***'1/age'*** in the weight model when MI was used, with a RBIAS of 12.5% for ***'ln (age)'***. The MI method using height measurements also produced large RBIAs values for the coefficient of ***'1/age'*** (RBIAS>10%). In general, the model for girls had larger RBIAS values than the corresponding model for boys.

As expected, the mean square errors (MSE) from the MI method were bigger than those from the ACA method, producing relative MSE that were greater than 1, and similarly RI produced MSE that were smaller than those from ACA method (Table 5.7). As with bias in the parameter estimates (Table 5.6), the relative MSE from the weight model for MI were larger than those for the height model, indicating larger variations in the imputation of weight measurements which could largely be due to the non-monotonic nature of weight measurements ($1.27 < RRMSE_{weight} < 1.35$ vs $1.14 < RRMSE_{height} < 1.15$).

Table 5.6 Relative bias in parameter estimates for model fitted to actual missing measurements in the BH Cohort.

		ACA		REGRESSION IMPUTATION			MULTIPLE IMPUTATION		
	Coefficient	Estimate	S.E	Estimate	S.E	RBIAS	Estimate	S.E	RBIAS
WEIGHT									
Girls	B_0	7.15	0.377	7.15	0.219	0	7.41	0.394	3.63
	B_1[age]	0.22	0.006	0.22	0.005	0	0.22	0.006	0
	B_2 [lnage]	-0.63	0.155	-0.63	0.101	0	-0.69	0.164	**9.52**
	B_3[1/age]	-0.008	0.001	-0.008	0.001	0	-0.009	0.002	**12.5**
Boys	B_0	7.65	0.316	7.65	0.177	0	7.75	0.448	1.31
	B_1[age]	0.21	0.005	0.21	0.004	0	0.21	0.005	0
	B_2 [lnage]	-0.48	0.128	-0.48	0.081	0	-0.52	0.169	**8.3**
	B_3[1/age]	-0.008	0.001	-0.008	0.001	0	-0.008	0.002	0
HEIGHT									
Girls	B_0	44.72	1.991	44.73	1.342	0.02	45.61	2.166	1.99
	B_1[age]	0.40	0.011	0.40	0.009	0	0.41	0.011	2.50
	B_2 [lnage]	8.80	0.628	8.80	0.432	0	8.53	0.686	3.07
	B_3[1/age]	1.24	4.226	1.22	2.61	1.61	1.05	4.429	**15.3**
Boys	B_0	44.54	1.599	44.54	1.073	0	44.72	2.000	0.40
	B_1[age]	0.37	0.009	0.37	0.007	0	0.37	0.010	0
	B_2 [lnage]	9.59	0.500	9.59	0.341	0	9.50	0.622	0.94
	B_3[1/age]	4.22	3.457	4.22	2.077	0	3.34	4.453	4.26
RBIAS>5%						0%			**25 %**

Table 5.7 Comparisons of the RRMSE from actual missing data.

	ACA		REGRESSION IMPUTATION			MULTIPLE IMPUTATION		
	Estimate	S.E	Estimate	S.E	RRMSE	Estimate	S.E	RRMSE
BH cohort								
MSE^{Gw}	2.872	0.161	2.177	0.106	0.87	4.62	0.394	1.27
MSE^{Bw}	2.455	0.130	1.866	0.084	0.87	4.461	0.249	1.35
MSE^{Gh}	4.962	0.345	3.733	0.220	0.87	6.538	0.427	1.15
MSE^{Bh}	3.984	0.246	2.961	0.155	0.86	5.712	0.385	1.14
Lungwena								
MSE^{Gw}	0.76	0.018	0.70	0.016	0.96	1.02	0.038	1.16
MSE^{Bw}	0.67	0.015	0.63	0.014	0.97	0.87	0.028	1.14
MSE^{Gh}	7.46	0.177	6.88	0.156	0.96	8.88	0.258	1.09
MSE^{Bh}	6.18	0.143	5.77	0.129	0.97	7.45	0.178	1.10

- All RRMSE calculated relative to the Available Case Analysis.
- Gw: Girls weight model Gh: Girls height model
- Bw: Boys weight model Bh: Boys height model
- Multiple Imputation produced larger MSEs relative to MSEs from ACA method, leading to RRMSE that are greater than 1.
- Regression Imputation produced MSE values that were smaller than MSE from ACA method, leading to RRMSE that were less than 1.

5.2.2 Modelling using the Lungwena cohort

Similar to results from BH Cohort, there were no significant differences in the parameter estimates between the RI method and the ACA method in both weight and height models, with all RBIAS values<1 % (Table 5.8). However, unlike the BH cohort, the RBIAS values from MI methods were also very small (all values <5%), indicating more precision in estimation of parameters in the Lungwena cohort.

Consistent with results from the BH cohort, the Mean square errors (MSE) from the MI method were bigger than those from the ACA method, producing relative MSE that were greater than 1, and similarly the RI produced MSE that were smaller than those from the ACA method (Table 5.7). Consistent with BH cohort results, the relative MSE from the weight model for MI were larger than those for the corresponding height model, indicating larger variations in the imputation of weight measurements ($1.14 < RRMSE_{weight} < 1.16$ vs $1.09 < RRMSE_{height} < 1.10$). However, the bias in these was not as large as what was observed in BH cohort.

Table 5.8 RBIAS of estimates for model fitted to actual missing data in the Lungwena Cohort.

		ACA		REGRESSION IMPUTATION			MULTIPLE IMPUTATION		
	Coefficient	Estimate	S.E	Estimate	S.E	RBIAS	Estimate	S.E	RBIAS
WEIGHT									
Girls	B0	4.53	0.067	4.53	0.065	0	4.53	0.069	0
	B1[age]	0.136	0.002	0.136	0.002	0	0.139	0.002	2.2
	B2 [lnage]	0.675	0.015	0.675	0.014	0	0.661	0.018	2.1
	B3[1/age]	0.003	0.001	0.003	0.001	0	0.003	0.001	0
Boys	B0	4.84	0.067	4.84	0.066	0	4.86	0.069	0.4
	B1[age]	0.136	0.002	0.136	0.002	0	0.136	0.002	0
	B2 [lnage]	0.761	0.014	0.761	0.013	0	0.754	0.016	0.9
	B3[1/age]	0.004	0.001	0.004	0.001	0	0.004	0.001	**0**
HEIGHT									
Girls	B0	53.10	0.198	53.10	0.193	0	53.10	0.195	0
	B1[age]	0.472	0.004	0.472	0.004	0	0.472	0.004	0
	B2 [lnage]	3.96	0.048	3.96	0.046	0	3.96	0.053	0
	B3[1/age]	0.023	0.001	0.023	0.001	0	0.022	0.001	4.3
Boys	B0	54.37	0.213	54.37	0.210	0	54.36	0.203	0
	B1[age]	0.469	0.004	0.469	0.004	0	0.470	0.004	0.2
	B2 [lnage]	4.07	0.042	4.07	0.041	0	4.05	0.046	0.5
	B3[1/age]	0.024	0.001	0.024	0.001	0	0.024	0.001	0
RBIAS>5%						0%			0%

CHAPTER 6: GROWTH VELOCITY AND ADOLESCENT OBESITY

This chapter deals with results of the empirical research question of the thesis. Presented in section 6.1 is the paper publication which is examining the relationship between early child growth velocity and early adolescent obesity, using mixed effects modelling. As outlined in the previous chapter, mixed effects modelling is flexible and allows for modelling of unbalanced longitudinal data. The unbalanced data can arise due to missing data or by study design. The original publication has also been included as Appendix 3.

6.1 PAPER 3

Title: Postnatal growth velocity and overweight in early adolescents: A comparison of rural and urban African boys and girls.

Published in the

American Journal of Human Biology: 2014 Jun; 26(5): 643-651

INTRODUCTION

Several studies have shown the association between early childhood growth and later health outcomes such as diabetes, cardiovascular diseases and obesity (Adair, 2007, Adair et al., 2009, Cameron and Demerath, 2002, Cameron et al., 2003). In particular, studies have examined the critical periods in infancy and early childhood that are associated with these health outcomes (Black and Krishnakumar, 1999, Botton et al., 2008, McCarthy et al., 2007, Ridgway et al., 2009).

Both growth retardation and rapid growth in the different stages of early life are predictive of the later health outcomes (Cameron and Demerath, 2002, Cameron et al., 2005, Li et al., 2003, Stein et al., 2010). For example, Flexeder et al. (2012) found that rapid weight gain in infancy is associated with physician-diagnosed asthma in school-aged children (Flexeder et al., 2012). A number of studies have examined the relationship between early growth and later health outcomes in high income as well as low and middle income countries. (Li et al., 2003, Martorell et al., 1995, Mesa et al., 2010, Ong et al., 2000, Salonen et al., 2009, Stein et al., 2010). However, there have also been inconsistent findings regarding the relationship between growth retardation, or stunting and overweight and obesity in later life. While it has been suggested that childhood under-nutrition predisposes a child to weight gain in later life (Hoffman et al., 2000), other studies have found that childhood stunting was associated with lower BMI (Schroeder et al., 1999, Walker et al., 2007) .

Several studies have also shown the short term and long term benefits of rapid growth for children in resource-poor settings (Hoddinott et al., 2008, Kalanda et al., 2005b, Victora et al., 2008, Victora et al., 2001). The short term benefits include, reduced morbidity and mortality, and improved cognitive development, while long term benefits include improved human capital and improved reproductive outcomes in women.

Although a wide body of evidence supports the long term benefits and detrimental effects of early rapid growth in low and middle income countries, few studies have looked at this relationship in a sub-Saharan African context, due to the limited number of birth cohort studies. Thus, this study compared the growth velocities of two cohorts from rural and urban African settings, and examined the relationship between size at birth (birth weight), growth velocity in infancy and early childhood, and early adolescent obesity. The two cohorts are likely to be at different stages of nutritional transition, considering the rural cohort is from a very low income country while the urban cohort is from a middle income country. Urbanisation is generally linked to changes in lifestyle factors that affect obesity risk, such as dietary patterns and sedentary behaviours. Thus apart from the nutritional differences, there may also be social, cultural, economic and environmental differences between the two cohorts that may affect growth and development of the children and also affect their risk of obesity.

Mixed-effects modelling and childhood structural growth model were used to examine the relationship between postnatal growth velocity and obesity or stunting in early adolescence (ages 9-11 years). Mixed-effects modelling is flexible in dealing with unbalanced longitudinal measurements, and takes into account correlations between repeated measurements. The use of the structural growth curve will allow for the estimation of the growth rates at any given age.

SUBJECTS AND METHODS

Weight and height measurements from 2 African longitudinal cohorts were used. The Bone-Health (BH) Study is a sub-sample of the Birth-to-Twenty (BH) birth cohort in Johannesburg, South Africa, which includes 453 black participants. The cohort has anthropometric measurements at birth, 3 months, 6 months, 1 year, 2 years, 4 years, 5 years, 7/8 years, 9 years, and 10 years. Birth weights were extracted from birth records, while subsequent weight/height

measurements were obtained using standard anthropometric techniques (Cameron, 1984). More specific details about this urban bone health cohort are reported elsewhere (Cameron et al., 2003, Cameron et al., 2005).

The rural component of the study used the Lungwena Child Survival Study (LCSS), which is a cohort of about 729 children living in Mangochi, a rural district in southern Malawi. The on-going study has growth data of children from birth to 16 or 17 years of age. The anthropometric data in this cohort were collected monthly from birth until 18 months, 3 monthly until 60 months, then at 6 years, 8-9 years, 10 years, 12 years and 15 years. Weight and height were measured during home visits, using portable spring-scales and self-made length boards, having reading increments of 100g and 5mm, respectively. More specific details for the Lungwena cohort are reported elsewhere (Espo et al., 2002, Maleta et al., 2003b).

In both cohorts, growth velocities were derived from a structural growth model fitted to growth data from birth to 60 months. The exclusion criteria and the overall number of participants available for analysis are shown in Figure 3.4 in Section 3.2.3.1.

Due to differences in the socio-economic status (SES) variables collected in the two cohorts, an SES score was calculated separately for each cohort. The SES variables in the BH cohort included household assets such as car, TV, fridge and washing machine, and household facilities such as type of water system, toilet type and electricity. The SES variables for the Lungwena cohort included ownership of land, farm animals, bicycle, and radio, amongst others and household variables such as maternal and paternal literacy level. In each cohort, an asset score was initially derived based on household assets. Principal component analysis was then used to derive an overall SES score by combining the asset score with other household and community SES variables.

Detailed description of the model and methods for deriving growth velocity have been explained in the Methods section of the thesis (section 3.2.3.1).

Previous analyses have shown this model to have optimum fit to the BH cohort growth data (Chirwa et al., 2014). The model was used to describe growth patterns in early childhood after adjusting for maternal characteristics (maternal height and age), SES and gestational age. Separate models were fitted for boys and girls in each cohort. The first order derivative of the model was then used to derive weight and height velocities over time (Mook-Kanamori et al., 2011, Botton et al., 2008). The growth velocity function was then used to derive the peak weight velocity (PWV), peak height velocity (PHV) and the age at which a child reached its peak weight velocity (APWV) and its peak height velocity (APHV). The primary outcomes were BMI and the proportion of children who were overweight in the 9-11 year age group. BMI cut-off charts for children were used to calculate corresponding overweight cut-offs (Cole et al., 2000, Cole et al., 2007).

The derived parameter estimates, growth velocity, infant peak velocity and the age at peak velocity were used as predictors of adolescent BMI or obesity. T-tests were used to compare weight, height growth velocity, peak growth velocity between boys and girls within and between cohorts. Linear regression was used to examine the relationship between BMI-for-age z-scores (BMIZ) in late childhood and early adolescence (9-11 years) and predictors, adjusting for birth weight, sex and cohort differences. Logistic regression was then used to explore predictors of obesity, adjusting for cohort differences and birth weight. Analysis was done using Stata Version 11, and all statistical tests were performed at 5% significance level.

The BH study was approved by the Human Research Ethics Committee of the University of Witwatersrand, while the Lungwena Child survival Study was approved by the Malawi National Health Science Research Committee.

RESULTS

Descriptive Statistics.

The proportion of boys in the BH cohort was higher than that of girls (57% vs. 43%), while the proportion of boys and girls in the Lungwena cohort was almost the same (51% vs. 49%). Of the 216 children in the BH cohort, almost half were first born, while only 19% of the 341 children from the Lungwena cohort were first born. The average maternal age for the BH cohort was 25 yrs. (with standard deviation of 5.9), while the average age in the Lungwena cohort was 26 years (sd=6.5). BH cohort mothers were on average taller than their Lungwena counterparts (158 cm vs 155 cm).

Table 6.1 shows the mean anthropometric measurements in infancy/early childhood and late childhood/early adolescence between boys and girls in the two cohorts. There were no significant differences in the average size at birth between the cohorts (p-values >0.05). However BH boys and girls experienced more rapid weight gain from 3 months onwards as shown by the significant differences in mean weight from 3 months, with BH boys and girls weighing on average more than their Lungwena counterparts. Although there were no data on birth length for the BH cohort, subsequent measurements showed BH boys and girls were on average significantly taller than their Lungwena counterparts.

In early adolescence, there were no significant differences in weight, age, height or BMI between boys and girls within each cohort, but there were significant differences between the cohorts, with BH boys and girls having higher mean BMI, height and weight compared to the

Lungwena boys and girls. However, unlike the pattern in infancy/early childhood, girls in the BH cohort were on average taller and weighed more than boys at ages 9/10 years. Figure 6.1 shows the distribution of BMI for boys and girls in the two cohorts, with BH children having largely higher BMI than Lungwena children. However, there is also wider variation in the BMI values in the BH cohort.

Average model parameter and growth velocity estimates.

Parameter estimates for weight and height models were derived for each child using the random components of the mixed models. A t-test comparison of these parameter estimates showed significant differences in the average parameter estimates between BH boys and Lungwena boys for both the height and weight growth model (Table 6.2). Similar results were also found amongst the girls from the 2 cohorts. BH boys had the highest starting values ($\alpha_{w\ \&}$ $\alpha_{h)}$, as well as the highest linear growth rates ($\beta_{w\ \&}\ \beta_{h)}$. However the α_h for the height model for both cohorts represents starting height/length at 3 months, due to the BH cohort not having height/length measurements at birth. Within each cohort, there generally were no significant differences in model parameter estimates between boys and girls in both cohort except for β_w and β_h in the Lungwena cohort. Non-significant difference in the linear component of the velocity curve between boys and girls in the Lungwena cohort was also shown by the non-significant differences in both weight and height velocities. There were significant differences in the weight velocity between boys and girls in the BH cohort except at 24 months. Although boys in the Lungwena cohort tended to have higher weight velocities than girls, there were no significant differences in average weight velocity between boys and girls in the Lungwena

cohort from 12 months onwards. Boys in the BH cohort generally exhibited higher height velocities than girls, with significant differences in the average height velocity between boys and girls in the first 2 years of life ($p<0.001$).

As expected and consistent with the changes in average weight and height over time, as shown in Table 6.1, weight and height velocities were highest in the first 12 months, with growth rates rapidly declining from 12 months (Table 6.2). There were no significant differences in the average weight velocities between small for gestational age (SGA) infants (WAZ at birth < -2) and appropriate for gestational age (AGA) infants (data not shown). Similar results were found when comparing those with low birth weight (birth weight <2.5kg) to those with normal birth weight (data not shown).

The significant differences in the parameter estimates between BH boys and Lungwena boys as well as between girls in the 2 cohorts were also shown by the significant differences in the weight and height velocities between the cohorts, with the BH boys having higher growth rates than their Lungwena counterparts. Similarly, BH girls exhibited higher growth rates than Lungwena girls. A strong positive linear relationship between weight and height velocity ($r=0.89$, $p<0.001$) was observed.

BH girls had the highest infancy peak weight velocity (1.39 kg/mo.). However, no significant difference was observed in the infancy peak weight velocity (PWV) or peak height velocity (PHV) between sexes within each cohort or between cohorts. BH boys which had the smallest PWV also had the youngest age at peak weight velocity (APWV). BH boy's height velocity

also peaked earliest compared to the other 3 groups. However, all velocities for the 4 groups peaked before 6 months.

Table 6.1 Comparison of physical growth measurements between boys and girls in the two cohorts.

	Bone Health			Lungwena				
	n	Boys	Girls	n	Boys	Girls	Sig[1]	Sig[2]
Birth and early childhood								
Weight (kg)								
Birth weight	216	3.2 ± 0.5	3.1 ± 0.4	341	3.3 ± 0.5	3.2 ± 0.5	0.115	0.070
3 mo.	82	6.5 ± 0.8	5.8 ± 0.7	274	6.0 ± 0.8	5.5 ± 0.7	<0.001	<0.001
6 mo.	52	8.1 ± 0.9	7.4 ± 1.0	286	7.2 ± 1.0	6.6 ± 0.9	0.011	<0.001
1 yr.	193	9.7 ± 1.4	9.2 ± 1.3	302	8.4 ± 1.1	8.0 ± 1.1	0.012	0.002
2 yr.	153	11.8 ± 1.7	11.4 ± 1.4	308	10.5 ± 1.4	10.1 ± 1.3	0.126	0.010
4 yr.	210	15.5 ± 1.9	14.9 ± 1.8	326	14.6 ± 1.5	14.0 ± 1.6	0.021	<0.001
5 yr.	187	18.6 ± 2.0	17.9 ± 2.1	338	16.0 ± 1.8	15.5 ± 1.9	0.022	0.016
Height (cm)								
Birth Length	-	-	-	341	48.9 ± 2.2	47.9 ± 2.1	-	<0.001
3 mo.	82	60.8 ± 2.9	58.7 ± 2.8	274	57.3 ± 2.4	56.1 ± 2.6	0.001	<0.001
6 mo.	52	66.3 ± 2.8	63.4 ± 4.1	286	62.5 ± 2.6	60.6 ± 2.6	0.015	<0.001
1 yr.	187	74.4 ± 3.1	72.6 ± 3.0	302	69.0 ± 2.6	67.8 ± 2.6	<0.001	<0.001
2 yrs.	143	83.6 ± 3.7	82.2 ± 3.1	308	78.2 ± 3.7	76.9 ± 3.4	0.010	0.002
4 yrs.	210	99.2 ± 3.9	97.9 ± 3.9	326	93.9 ± 4.3	92.4 ± 4.4	0.017	0.002
5 yrs.	187	108.8 ± 4.0	107.4 ± 4.2	338	100.9 ± 4.4	99.4 ± 4.7	0.022	0.003
Early Adolescence								
Age (yrs.)	216	10.5 ± 0.3	10.5 ± 0.3	341	10.3 ± 0.3	10.35± 0.3	<0.001	0.011
Height (cm)	216	137.8 ± 6.1	138.4 ± 5.9	341	129.7± 5.5	128.46 ± 6.0	<0.001	<0.001
Weight (kg)	216	32.9± 6.2	33.4 ± 6.6	341	25.7 ± 3.2	25.22 ± 3.5	<0.001	<0.001
BMI (kg/m^2)	216	17.3± 2.5	17.4 ± 2.9	341	15.3 ± 1.2	15.22 ± 1.2	<0.001	<0.001
Overweight (%)		26(21%)	22(24%)		2(1.2%)	0(0%)	<0.001	<0.001
Underweight (%)		1(0%)	5(5%)		13(8)	17(10%)	<0.001	0.246

Sig[1]: BH boys vs. Lungwena boys. All mean comparisons done using t-test.

Sig[2]: BH girls vs. Lungwena girls. All proportions comparisons done using Fishers' exact test.

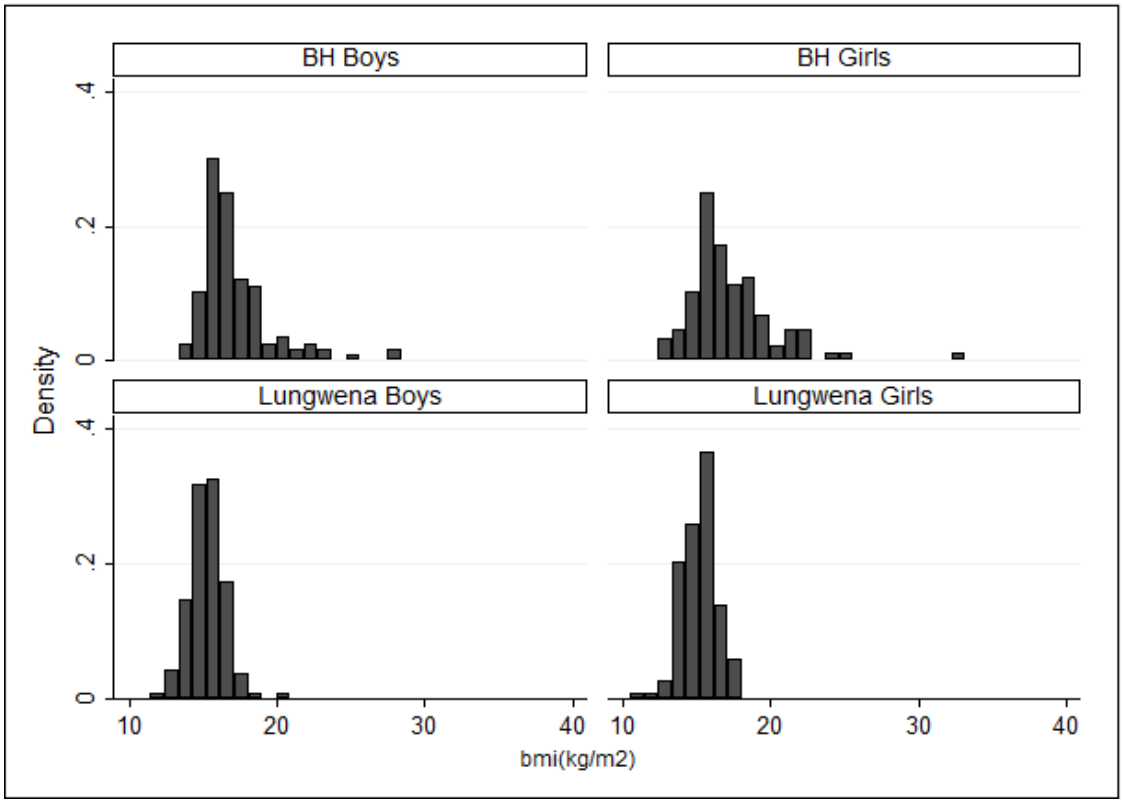


Figure 6.1 BMI in early adolescence for boys and girls in the two cohorts.

Table 6.2 Average differences in estimates, growth and peak velocity between cohort and sex.

	BH COHORT		LUNGWENA COHORT		Coh. Dif.		Sex dif.	
	Boys	Girls	Boys	Girls	M	F	BH	LUN
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	sig	sig	sig	Sig
Parameters (weight)								
α_w	6.70 (0.45)	4.44 (0.34)	5.49 (0.66)	5.13 (0.63)	**	**	**	**
β_w	0.16 (0.02)	0.13 (0.03)	0.14 (0.02)	0.14 (0.03)	**	0.023	**	0.816
γ_w	0.42 (0.02)	1.16 (0.03)	0.54 (0.02)	0.48 (0.03)	**	**	**	**
δ_w	-3.50 (0.03)	-1.36 (0.03)	-2.68 (0.03)	-2.43 (0.03)	**	**	**	**
Parameters (height)								
α_h	66.5 (2.07)	56.4 (1.95)	54.1 (2.28)	53.5(2.20)	**	**	**	0.030
β_h	0.59 (0.04)	0.52 (0.06)	0.52 (0.06)	0.52 (0.07)	**	0.815	**	0.654
γ_h	1.37 (0.03)	4.42 (0.06)	3.79 (0.07)	3.56 (0.08)	**	**	**	**
δ_h	-39.8 (0.04)	-22.6 (0.05)	-15.3 (0.06)	-16.8 (0.08)	**	**	**	**
Peak Velocity								
PWV	1.31 (0.26)	1.39 (0.28)	1.36 (0.24)	1.35 (0.29)	0.067	0.217	0.024	0.579
APWV (mo.)	2.49 (0.02)	2.86 (0.05)	3.10 (0.06)	2.96 (0.07)	**	**	**	**
PHV	5.77 (0.37)	5.59(0.58)	5.51 (0.67)	5.53 (0.84)	**	0.556	0.006	0.882
APHV (mo.)	5.00 (0.08)	7.24 (0.34)	6.92 (0.47)	5.43 (0.27)	**	**	**	**
Weight velocity (kg/mo.)								
3 m	0.48 (0.03)	0.50 (0.03)	0.44 (0.03)	0.41 (0.03)	**	**	**	**
6 m	0.29 (0.03)	0.33 (0.03)	0.27 (0.03)	0.26 (0.03)	**	**	**	**
12 m	0.21 (0.03)	0.23 (0.03)	0.20 (0.03)	0.19 0.03)	**	**	**	0.056
24 m	0.18 (0.02)	0.18 (0.03)	0.17 (0.02)	0.17 (0.03)	**	**	0.795	0.431
48 m	0.17 (0.02)	0.16 (0.03)	0.15 (0.02)	0.15 (0.03)	**	0.103	0.002	0.796
60 m	0.17 (0.02)	0.15 (0.03)	0.15 (0.02)	0.15 (0.03)	**	0.540	**	0.873
Height Velocity (cm/mo.)								
3 m	3.34 (0.17)	2.99 (0.14)	2.41 (0.10)	2.45 (0.11)	**	**	**	0.002
6 m	1.61 (0.07)	1.62 (0.07)	1.37 (0.08)	1.37 (0.09)	**	**	0.221	0.468
12 m	0.94 (0.05)	1.00 (0.07)	0.91 (0.07)	0.89 (0.09)	**	**	**	0.144
24 m	0.71 (0.04)	0.73 (0.06)	0.70 (0.07)	0.69 (0.09)	0.134	**	**	0.211
48 m	0.64 (0.04)	0.63 (0.06)	0.61 (0.06)	0.60 (0.08)	**	0.015	0.019	0.352
60 m	0.63 (0.04)	0.60 (0.06)	0.58 (0.06)	0.58 (0.08)	**	0.123	**	0.393

M = BH boys vs Lungwena boys
BH = BH boys vs BH girls
PWV= Peak weight velocity (kg/mo.)
PHV= Peak height velocity (cm/mo.)
All comparisons done using the t-test.

F = BH girls vs Lungwena girls
LUN = Lungwena boys vs Lungwena girls
APWV = Age at peak weight velocity (month)
APHV= Age at peak height velocity (month)
**:- p-value <0.001

Relationship between birth weight, growth velocity, peak velocity and adolescent BMI

There were no significant correlations between birth weight and weight velocity (r=-0.08, p-value= 0.06) or height velocity (r=-0.05, p-value=0.27).

There was a positive but weak relationship between birth weight and adolescent BMI, with birth weight only explaining 1% of the variation in BMI (Table 6.3). This relationship did not change even after adjusting for sex differences. However, when cohort differences were taken into account, the total variation explained by the model increased from 1% to 24%, signifying the large differences that exist between the 2 cohorts. The effect of birth weight on BMI was also supported by the results from the relationship between α for the weight model and BMI, with no significant sex difference being observed. Within each of the 3 models using parameter estimates from weight models, β_w had the strongest linear relationship with BMI compared to the other 3 parameter estimates, with no linear relationship being observed between adolescent BMIZ and *DW*. Both γ_w and δ_w were non-significant when effect of cohort difference was taken into account.

There was a negative linear relationship between adolescent BMIZ and APWV, indicating that infants that reached their peak weight velocity early were more likely to have high BMI in adolescence. A strong negative correlation was also observed between PWV and APWV (r=-0.53, p-value <0.001), indicating that infants with low PWV were more likely to reach their peak later than infants that exhibited high PWV. Even though there was a strong relationship between peak weight velocity and adolescent BMIZ, this relationship became non-significant when the age at which the infant reached its peak velocity was taken into account (p-value $_{(unadjusted)}$ = 0.004, p-value $_{(adjusted)}$ = 0.31)). Peak height velocity was not correlated with

adolescent BMIZ. Even though, there was a significant linear relationship between adolescent BMIZ and age at which the infant reached peak height velocity, this relationship become non-significant when cohort differences were taken into account (model 3).

There was a general decrease in the relationship between weight velocity and adolescent BMIZ over time even after adjusting for birth weight ($R^2_{(3m)}$ =0.38, $R^2_{(60m)}$ =0.29). Even though there was a strong relationship between adolescent BMIZ and height velocity in the first 6 months, even after adjusting for birth weight, as observed from the R^2 values (models 1 & 2), there were no differences in the strength of the relationship over time when cohort and sex differences were taken into account (model 3).

Table 6.3 Relationship between adolescent BMI and growth, peak velocity and model parameters.

Main Predictor	Model 1 β (SE)	R^2	Model 2 β (SE)	R^2	Model 3 β (SE)	R^2
Sex : Boys	Ref					
Girls	-0.18 (0.09)†	0.01				
Cohort: BH	Ref					
LUN	-1.07 (0.08)	0.22				
Birth weight	0.27 (0.10)	0.01				
Parameters (weight)						
α_w	0.34 (0.05)	0.08	0.33 (0.05)	0.08	0.25 (0.06) †	0.27
β_w	21.2 (1.55)	0.25	21.3 (1.61)	0.25	18.9 (1.45)	0.42
γ_w	0.96 (0.18)	0.05	1.00 (0.18)	0.07	0.31 (0.21) †	0.25
δ_w	-0.05 (0.07) †	0.001	-0.04 (0.07) †	0.01	0.06 (0.09) †	0.25
Parameters (height)						
α_h	0.08 (0.01)	0.15	0.07 (0.01)	0.15	0.001(0.013) †	0.25
β_h	4.32 (0.62)	0.08	4.18 (0.63)	0.08	2.20 (0.60)	0.26
γ_h	-0.24 (0.04)	0.05	-0.24 (0.04)	0.06	0.017 (0.05) †	0.25
δ_h	-0.05 (0.01)	0.16	-0.05 (0.002)	0.18	0.001 (0.01) †	0.25
Infant Peak Velocity						
PWV	1.85 (0.16)	0.20	1.84 (0.16)	0.20	1.86 (0.14)	0.44
PHV	0.35 (0.07)	0.05	0.33 (0.07)	0.05	0.23 (0.06)	0.26
APWV	-1.33 (0.19)	0.08	-1.39 (0.19)	0.10	1.32 (0.29)	0.27
APHV	-0.004 (0.05) †	0.001	-0.008 (0.05) †	0.01	0.05 (0.04) †	0.24
Weight velocity						
3 m	14.8 (0.80)	0.38	14.7 (0.81)	0.38	12.3 (1.05)	0.40
6 m	18.3 (1.03)	0.36	18.2 (1.04)	0.36	14.8 (1.23)	0.40
12 m	21.7 (1.28)	0.34	21.7 (1.31)	0.34	17.4 (1.37)	0.42
24 m	23.5 (1.43)	0.33	23.7 (1.47)	0.33	19.3 (1.42)	0.43
48 m	23.3 (1.50)	0.30	23.5 (1.55)	0.30	19.6 (1.44)	0.43
60m	22.5 (1.52)	0.29	23.1 (1.57)	0.29	19.5 (1.44)	0.43
Height velocity						
3 m	1.31(0.10)	0.24	1.32 (0.10)	0.25	0.81 (0.25)	0.26
6 m	3.68 (0.29)	0.22	3.68 (0.29)	0.24	1.86 (0.50)	0.26
12 m	3.79 (0.54)	0.08	3.72 (0.55)	0.09	1.50 (0.54)	0.26
24 m	3.67 (0.65)	0.05	3.54 (0.65)	0.06	2.22 (0.59)	0.26
48 m	4.07 (0.66)	0.06	3.93 (0.66)	0.07	2.32 (0.61)	0.26
60m	3.98 (0.65)	0.06	3.83 (0.67)	0.07	2.30 (0.61)	0.26

Model 1: Adolescent BMI vs main predictor
Model 2: Adolescent BMI vs main predictor (adjusting for birth weight).
Birth weight was non-significant when adjusted for the main predictors in Model 2.
Model 3: Adolescent BMI vs main predictor (adjusting for birth weight, sex and cohort differences)
R^2 = total variation in BMI explained by the overall model
†: effect of main predictor was not significant

Relationship between birth weight, growth velocity, peak velocity and adolescent obesity

Table 6.4 shows the association between adolescent overweight and growth velocity. The study found no association between sex and being overweight adolescent, even though girls had lower odds of being overweight compared to boys (OR= 0.88, p-value= 0.671).. The Lungwena cohort had lower odds of being overweight than the BH cohort (OR=0.02, p-value<0.001). The odds did not change even after adjusting for sex differences. Even though the odds of being overweight increased with increase in birth weight, the association was not significant (OR=1.25, p-value=0.486)

Consistent with the observed relationship between BMI and linear growth rates in weight (β_w) as shown in Table 6.3, the study also found strongest association between being overweight and linear growth rate in weight (β_w), even after adjusting for cohort differences and birth weight (OR= 2.05, p-value <0.001). While there was a strong association between being an overweight adolescent and a child's estimated baseline weight (α_w), this relationship was not significant when cohort differences were taken into account. After adjusting for cohort differences and birth weight, only the linear growth rate function (β_w) was found to be associated with adolescent overweight.

The study also found strong association between adolescent overweight and linear growth rates in height, with children exhibiting faster height growth rates being more likely to be overweight in adolescence. However this relationship was non-significant when cohort differences were taken into account. Consistent with weight model parameters, baseline height (α_h) and the decrease in height velocity over time (γ_h) were also not associated with being overweight.

The logistic regression models showed a stronger association between overweight in early adolescence (ages 9-11 years) and weight gain in infancy than with weight gain in early

childhood. At 3 months, every 1 standard deviation (SD) increase in weight velocity had a 8-fold odds of being overweight in early adolescence. These odds reduced with age such that by the time a child is 5 years old, every 1 SD increase in weight velocity resulted in almost 3-fold odds of being overweight. Even though there was a decrease in the odds of being overweight after adjusting for cohort differences and birth weight, the trend over time was the same. The same trend was observed with height velocity. However, there were no significant association between height velocity and being overweight after adjusting for birth weight and cohort differences. No association was found between obesity and peak height velocity, age at peak height velocity or age at peak weight velocity, when adjusted for cohort difference. However children with high peak weight velocity were more likely to be overweight in adolescence even after adjusting for cohort differences.

Table 6.4 Odds ratios for relationship between overweight and growth velocity, peak velocity and model parameters.

Main Predictor	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3‡ OR (95% CI)
Sex :boys	Ref		
:girls	0.88 (0.49, 1.58)†		
Cohort: BH	Ref		
LUN	0.02 (0.005, 0.09)		
Birth weight	1.25 (0.67, 2.34)†		
Parameters (weight)			
α_w	1.53 (1.19, 1.97)	1.55 (1.20, 2.02)	1.12 (0.89, 1.40)†
β_w	2.21 (1.65, 2.96)	2.27 (1.68, 3.08)	2.05 (1.46, 2.87)
γ_w	1.46 (1.24, 1.72)	1.48 (1.25, 1.75)	1.08 (0.92, 1.27)†
δ_w	1.06 (0.87, 1.29)†	1.07 (0.88, 1.31)†	1.05 (0.92, 1.21)†
Parameters (height)			
α_h	1.79 (1.46,2.21)	1.79 (1.45, 2.22)	0.88 (0.67, 1.15)†
β_h	1.71 (1.21, 2.42)	1.70 (1.20,2.41)	1.14 (0.77, 1.70)†
γ_h	0.74 (0.62, 0.89)	0.74 (0.62, 0.89)	1.05 (0.90, 1.24)†
δ_h	0.53 (0.43, 0.65)	0.53 (0.43, 0.65)	1.10 (0.84, 1.45)†
Infancy Peak velocity			
PWV	1.42 (1.08, 1.87)	1.42 (1.07, 1.88)	1.68 (1.17, 2.42)
PHV	1.58 (0.99, 2.52)†	1.56 (0.97, 2.50)†	1.44 (0.76, 2.74)†
APWV	0.06 (0.01, 0.12)	0.03 (0.01, 0.12)	4.31 (0.78, 23.7)†
APHV	0.99 (0.74, 1.35)†	0.99 (0.74, 1.34)†	1.17 (0.88, 1.55)†
Weight velocity			
3 mo.	7.49 (4.50, 12.46)	7.96 (4.68, 13.52)	4.80 (2.49, 9.26)
6 mo.	4.07 (2.82, 5.86)	4.09 (2.84, 5.90)	2.60 (1.77, 3.83)
12 mo.	3.51 (2.48, 4.94)	3.58 (2.52, 5.08)	2.46 (1.89, 3.61)
24 mo.	3.06 (2.20, 4.25)	3.18 (2.26, 4.47)	2.44 (1.68, 3.55)
48 mo.	2.67 (1.95, 3.66)	2.78 (2.01, 3.86)	2.41 (1.68, 3.64)
60 mo.	2.60 (1.90, 3.56)	2.71 (1.96, 3.75)	2.39 (1.65, 3.47)
Height velocity			
3 mo.	3.02 (2.19, 4.15)	3.01 (2.19, 4.14)	0.87 (0.50, 1.50)†
6 mo.	5.49 (3.27, 9.22)	5.52 (3.29, 9.24)	1.62 (0.61, 4.32)†
12 mo.	2.25 (1.60, 3.15)	2.25 (1.60, 3.16)	1.35 (0.89, 2.03)†
24 mo.	1.55 (1.13, 2.14)	1.54 (1.12, 2.13)	1.34 (0.88, 2.04)†
48 mo.	1.51 (1.10, 2.09)	1.50 (1.09, 2.07)	1.32 (0.86, 2.03)†
60 mo.	1.55 (1.12, 2.14)	1.53 (1.11, 2.13)	1.26 (0.82, 1.94)†

Model 1: Overweight vs main predictor
Model 2: Overweight vs main predictor (adjusting for birth weight)
Model 3: Overweight vs main predictor (adjusting for birth weight and cohort differences).
‡: not adjusted for sex due to limited number of children in Lungwena cohort with outcome.
†: effect of main predictor was not significant

DISCUSSION

This study has been able to demonstrate a positive linear relationship between rapid weight gain in infancy and early childhood and early adolescent BMI, as well to show a relationship between rapid growth in the early years and the odds of being overweight/obese in early adolescence.

The high odds ratio and R^2 values between growth velocity in the first year of life (the period which was also characterised by high growth velocity) and adolescent BMI, highlight the association between rapid weight gain and obesity in early adolescence. The decreasing trend in the OR values in later early childhood highlights the critical period during infancy that is highly associated with adolescence/adult obesity. This supports what prior studies in the BH cohort and others elsewhere have found, albeit using different methods or measures (Adair et al., 2009, Cameron et al., 2003, Demerath et al., 2009, Ekelund et al., 2007, Stein et al., 2010, Botton et al., 2008, McCarthy et al., 2007). In a study of the relationship between rapid weight gain in the first 2 years of life and obesity in childhood in BH children with appropriate birth weight for gestational age (AGA), Cameron et al (2003), using weight-for-age z-scores, found that children that exhibited rapid growth in infancy were significantly taller, and weighed more in childhood. Our study has been able to demonstrate this using parameter estimates from the Reed1 model, with the parameter β_w, a function related to growth velocity being highly positively associated with early adolescent BMI. Consistent with the study by Mook-Kanamori and colleagues, our study found high PWV to be highly associated with early adolescence overweight. The significance of the relationship between rapid weight gain in infancy and adolescent BMI was also highlighted by the negative association between APWV and adolescent BMI, indicating that infants that reached infant peak weight velocity early were more likely to have high BMI. Apart from that, our study has also explored the relation using

height velocity and extended the period to early adolescence (9-11 years). Our study has also been able to show the similar association between rapid growth and adolescent BMI in a rural population, which is from a predominately malnourished population, with high levels of stunting and underweight. The critical period of development is the same in both cohorts. However, the rapid infant growth in this rural population seems to have beneficial effects, as it protects the adolescent child from the effects of under-nutrition**,** with few cases of obesity.

There are several hypothesised biological relationships between prenatal and postnatal growth and obesity in later life, and a large body of evidence supports these hypothesised relationships (Adair, 2007, Chomtho et al., 2008, Druet et al., 2012, Ekelund et al., 2007, Jones-Smith et al., 2007, McCarthy et al., 2007, Ong and Loos, 2006). These previous studies showed that either small size at birth, small size at birth combined with fast growth or fast growth itself, have effects on later life health outcomes. Studies have also shown that low-birth-weight infants usually exhibit rapid growth during the first year of life (Adair, 2007, Johnson et al., 2012b, Ong, 2006). However, our study which used data from 2 cohorts from different settings in terms of environmental and socio-economic factors, found no relationship between size at birth (birth weight) and growth velocity in both cohorts. Similarly, we found no association between size at birth and overweight in early adolescence. Both birth weight and its estimated parameter (α_w) were not associated with adolescent overweight. The non-significant relationship between birth weight and growth velocity as well as with overweight in early adolescence could also be due to the limited range of birth weight measurements, since our sample excluded preterm babies. Even though there was a wide variation in the age of initial weight measurements for the Lungwena cohort, for babies not delivered in a health facility, the mixed effects model adjusted for the age at which the measurements were taken.

However, the effect of the differences in the environmental and socio-economic factors in the two cohorts were shown by the differences in the growth rates and the postnatal prevalence of stunting/underweight and overweight in the cohorts as well as the significance of cohort term in the models. Despite there being no significant differences in birth weights between the 2 cohorts, the urban BH children exhibited more rapid weight gain in the first year of life. This rapid weight gain was associated with a high prevalence of overweight adolescents in this population. The differences in the prevalence of overweight adolescents in the two cohorts, considering the non-significant differences in their size at birth, highlights the significance of rapid weight gain rather than birth size, in the relationship between early growth and obesity in adolescence, in this particular setting. These results are in support of the 'fast growth and obesity' hypothesis, rather than the 'size at birth' or the 'size at birth and fast growth' hypotheses. The relationship between faster growth velocity and obesity/overweight in later life, independent of birth weight, has been hypothesised to be mainly due to over-nutrition (Jones-Smith et al., 2013). The more rapid weight gain in the BH cohort relative to the Lungwena cohort may be due to nutritional and environmental differences, among other factors. The slower weight velocity in the Lungwena cohort, from as early as 3 months, could be due to poor maternal nutritional status and the early introduction of complementary foods. As Lungwena is predominately a poor rural community, the complementary foods used are likely to be of poor nutritional content and to expose the infants to pathogens (Espo et al., 2002).

Our results are in general consistent with study by Adair et al (2013), which also looked at association between weight and height gain, and adult health outcomes in 5 cohorts from LMIC (Adair et al., 2013). The study found a positive relationship between weight gain and adult BMI, with the strength of the relationship increasing with age at which measurement was taken. However, unlike our study, they also found positive relationship between birth weight

and adult BMI, and they also found a decreasing relationship between height gain and BMI. The variations in these results could be due to the differences in the age ranges used as well as the limited amount of observations at 3 and 6 months in the BH cohort of our study.

Apart from looking at cohorts from different SES and environmental settings, the other strength of this study is in the use of mixed effects modelling to model growth trajectories and to derive growth velocities. Mixed effects modelling allowed us to compare growth velocity at any age even though some of the data collection waves in the two cohorts were at different times. Our results are in general, consistent with results from other studies that have used mixed effects. In a study of Dutch children, Mook-Kanamori and colleagues, also using the Berkey-Reed model and mixed effects modelling, found that rapid weight gain in the first months was more associated with risk of overweight than catch-up growth ('size at birth and fast growth hypothesis') during the first 2 years (Mook-Kanamori et al., 2011). Similarly, Botton and colleagues, using the adapted Jenns-Bayley model and using mixed effects modelling, also found increased risk of obesity due to rapid growth in the first 6 months in French children (Botton et al., 2008). However, their study also found that this risk started increasing again from 3 years. However, they derived their growth velocity from a model fitted from birth to 10 years, which may have made it possible to pick out the increase in growth velocity from 3 years. Our study fitted the growth model up to 5 years only.

The main limitation of the study is unavailability of data on adolescent factors associated with BMI in one of the cohort, which could have been adjusted for in the relationship between postnatal growth and adolescent BMI/overweight. The other limitation for the study is the amount missing weight and height measurements during the first year of life in the BH cohort which could have affected the fitness of the growth model used for estimating growth velocity.

In conclusion, although our results support the hypothesis that rapid growth in infancy increases the risk of overweight/ obesity in later life, the long term effects of infancy rapid growth are dependent on the particular population's stage of nutrition transition. For a population in early stages of nutrition transition or with poor nutritional status, rapid growth in early childhood may have long term beneficial effects as was evidenced by the almost non-existent prevalence of overweight in the Lungwena cohort, despite some children exhibiting rapid growth in early childhood. On the other hand, for populations undergoing rapid nutrition transition as is the case with the BH cohort, rapid growth has detrimental long term effects, as was evidenced by the prevalence of overweight and obesity in early adolescence. To further explore the relationship between postnatal growth velocity and later health outcome, we would recommend modelling growth into adolescence and also include pubertal stages and SES factors during adolescence that are highly associated with BMI, such dietary patterns and physical activity behaviours of the adolescents in the cohorts. Further studies in similar cohorts in low- and middle-income countries (LMICs) might also help in explaining the effect of shifts in dietary and sedentary behaviours associated with urbanisation.

PART 4: SYNOPSIS

This part of the thesis consists of two chapters. Chapter 7 gives a summary of the thesis findings in relation to the four main objectives, and an overall thesis discussion. Chapter 8 looks at overall thesis recommendations, possible future research questions emerging from the thesis and overall thesis conclusions.

CHAPTER 7: THESIS KEY FINDINGS AND DISCUSSION

The following chapter summarises the thesis findings in relation to each of the objectives outlined in Chapter 1, and gives an overall summary of the thesis key findings. The second section of the chapter discusses the key findings of the thesis in relation to literature and the limitations of the study. The thesis findings have been ordered as per thesis objectives and chapters 4-6.

7.1 KEY FINDINGS

This section presents a summary of the statistical methods, results from the four main objectives of the thesis (Tables 7.1-7.3) and a summary of thesis key findings.

Table 7.1 Comparison of growth models using mixed effects modelling.

Thesis Objective 1	What was done	What was examined	What was found
Main Objective: To explore childhood growth curves that best describe infant and childhood growth in 2 African settings. **Specific objectives:** • Compare the fitness of different parametric and non-parametric childhood growth models. • Assess the effect of time interval between data collection waves on model fitness.	**Growth models fitted using LME** a) Structural models • Reed1 model • Count b) Non Structural models • 3rd Order Polynomial • 2nd Order Polynomial **Growth models fitted using NLME** c) Structural models • Jenss-Bayley • Adapted Jenss-Bayley **Model Convergence** d) Comparison of model convergence in the 2 cohorts.	**Appropriateness of model** • Covariance structure • Likelihood ratio test • Residual plots **Goodness of fit of model** • Akaike Information Criterion (AIC) • Bayesian Information Criterion (BIC) • Absolute median residuals • Absolute maximum residuals **Convergence problems** • Number of iterations before convergence. • Number of higher order terms added to random component before non-convergence.	• Fit of models affected by length of time between data collection waves, especially in first year of life. • Reed1 model had a better fit to both weight and height measurements. • Variations in how different models estimated initial weight or height. • Most models failed to pick out the pre-puberty rapid growth (at 7-9 years). • Non- convergence problem when higher order terms were added to the random component of the mixed model, especially with the weight models. • No significant variations in the age at which children in each cohort experienced deceleration in growth.

LME: Linear Mixed Effects modelling NLME: Non-Linear Mixed Effects modelling.

Table 7.2 Dealing with intermittent missing physical growth measurements

Thesis Objective 2	What was done	What was examined	What was found
Main objective: To compare statistical methods of dealing with missing data in longitudinal physical growth measurements. **Specific Objectives:** • To assess the efficiency of Available Case Analysis (ACA) method in dealing with missing data. • To assess the added value of Multiple Imputation (MI) in the analysis of missing physical growth data. • To assess the added value of growth model-based regression imputation in the analysis of missing physical growth data. • To assess the effect of time interval between data collection waves on the efficiency of the different methods of dealing with missing data.	**Simulated Missing data** • Complete Case Analysis • Available Case Analysis • Multiple Imputation • Growth model-based regression imputation (RI) **Actual missing data** • Available Case Analysis • Multiple Imputation • Growth model-based regression imputation (RI)	**Sensitivity Analysis** • Relative bias of growth model parameter • Relative mean square error (RMSE). • Percentage coverage. • Paired t-test of observed, regression predicted and multiple imputed mean height and weight.	• No significant differences in efficiency between using MI or ACA-based LME. • No significant differences in parameter estimates between regression imputation, ACA or MI estimates. • Regression Imputation method produced smaller standard errors than ACA-based LME, due to increased number of observations. • More bias in MI values if imputation model does not take into account the individual child's growth trajectory. • Bias in the estimated parameters consistently affected by the number of data points (amount of information from each child), with the Lungwena cohort parameters having reduced bias.

Table 7.3 Relationship between infant and early childhood growth velocity and early adolescent obesity.

Thesis Objective 3	What was done	What was examined	What was found
Main objective: To compare growth of children in rural and urban African settings. **Specific objectives:** • To compare infant growth velocity in the 2 different settings. • To examine the relationship between infant and early childhood growth velocity, and early adolescent BMI. • To examine the association between early adolescent obesity and infant growth rates.	• Growth velocity modelling • Multiple linear regression. • Logistics regression	**Growth velocity modelling** • Trends in growth velocity over time. • T-tests on growth model parameters, PWV, APWV, PHV, and APHV. **Multiple linear regression** • Model coefficient • R^2 statistic for linear relationship. • Residuals for model assumption diagnostics **Logistics regression** • Odds ratios for association	• High growth velocity in both cohorts in the first 2 years of life, with both cohorts reaching peak growth velocity in the first year of life. • Rapid growth in infancy, independent of size at birth (birth weight) highly associated with high BMI in early adolescent. • Rapid growth in infancy for an over-nourished setting is highly associated with early adolescent obesity. • Rapid growth in malnourished (under-nutrition) setting beneficial, as it protect the child from detrimental effects of under-nutrition (adolescent underweight).

7.2 SUMMARY OF KEY FINDINGS

- Model fitting affected by degree of imbalance (missing data), which can lead to failure by the model to pick out deceleration or inflection points (non-convergence of model when higher order terms are added to the random component of the model)
- Model fitting affected by the number of data collection waves and the interval between waves, resulting in failure to find solutions for higher order terms (deceleration terms) and can also lead to over-fitting of the model (too many unnecessary terms).
- Multiple Imputation of longitudinal growth measurements is greatly affected by the imputation model used. Care must be taken in defining an appropriate imputation model. It is necessary to define an imputation model that takes into account each child's growth trajectory.
- Available Case Analysis using LME performed very well in dealing with intermittent missing physical growth measurements.
- Empirically, rapid growth velocity in infancy for an under-nourished population has protective effect from adolescent underweight, but has a detrimental effect in over-nourished populations, leading to adolescent obesity.

7.3 EMERGING RESEARCH THEMES

The main empirical statistical issues that came out of the research were non-convergence of the growth models during model fitting, and the effect of the choice of imputation model when using Multiple Imputation to deal with missing data.

7.3.1 Model Convergence

The factors that affected convergence of the models as evidenced by results from the 2 cohort were type of measurements (height or weight) and the time interval between data points.

7.3.1.1 Type of measurements

Structural human growth models are defined as monotonic functions and tend to fit well to height or other skeletal measurements variables, which are monotonic. Applying these models to weight measurements may affect the convergence due to possible fluctuations of weight measurements over time since, unlike height, weight is not necessarily a monotonic function. Even though it is generally expected to increase over time, the fluctuations are not uncommon. For a child experiencing adverse events (illness or episodes of malnutrition), this can lead to fluctuations in weight over time. However, this might not be noticeable if data collection waves are far apart compared to when data waves are close together. Thus, studies have generally found that structural models fit fairly well to weight measurements because such measures are often spaced a reasonable distance apart. In this study, they tended to fit to height measurements better than to weight measurements.

7.3.1.2 Number of and Time Interval between data points

Even though the modelling period was the same for the 2 cohorts (birth to 10 years), the number of data points in the Lungwena Cohort was more than double the number of data points in the BT20 cohort. The large number of data points in the Lungwena cohort allowed for more of the higher order terms to be added to the random component part of the model without experiencing convergence problems. However, the study found no significant effect of adding the higher order terms apart from reducing the problem of non-convergence of the models. Higher order terms such as ln (age), 1/age, or age^2 in growth models generally represent deceleration in growth rates.

Despite the fact that Mixed effects modelling allows for unbalanced data caused by missing values or by design, the period between data collection waves can have an impact on the scale of non-balancedness. For a study with data collection waves far apart, a missing value would create a large time interval between the available data points. This unbalancedness, in turn, affects the convergence of the models, as the model struggles to pick out the deceleration or acceleration points. A significant deceleration term in the random component implies the model was able to find separate deceleration points (solutions) for each individual. If data points are far apart, the chances are that the deceleration will happen within the same interval.

The estimation of the growth curves were also affected by the intensity of data points in the first years of life. Comparison of actual mean weight or height at baseline and the estimated initial weight or height, represented by the constant terms in the models, also highlighted the effect of the number of data points on curve fit. In general, there was better estimation of initial values if there were more data points in the first years of life. However, the non-structural models were not as much affected by the limited information in the first year of life as the

structural models. This highlights the general problem that structural models have. Despite the advantage that the parameters of the structural models can be interpreted in terms of growth velocity and deceleration, their rigidity brings in challenges in prediction of measurements if data points in early years are far apart. The structural models struggle to pick out the rapid growth associated with this period if there is limited individual information.

Other studies have shown that using fractional polynomials can give better fit to growth measurements. However, as with other non-structural curves, the main disadvantage of this would be that the parameters are not biologically interpretable. Thus the choice of whether to use a structural or a non-structural growth curve would be motivated by the purpose behind the modelling.

7.3.2 Imputation Model for Multiple Imputation

The performance of an imputation model depends on the type of repeated measures (profile/ trajectory) and the distribution of the variables as well as the missing data mechanism. In a study to compare performance of different methods, Tang et al. (2005) found that the multivariate normal (MVN) method, which was used in the present study, performed well if variables were not highly skewed (Tang et al., 2005). They also found that ACA showed high bias if data departed from MAR and MI techniques performed better than ACA, under such conditions. In the present study, it was assumed that data were MAR and as expected it was found that both MI and ACA performed similarly well under a given scenario (i.e. in each cohort). The differences in the number of data points affected both methods similarly.

The differences in bias in MI parameter estimates between the 2 cohorts could also have been due to the differences in the amount of information used in the modelling process due to differences in sample size and number of data points between the 2 cohorts. Tang (2005) also

found that a larger sample size affected the performance of the imputation model, with its effect being reduced if sample size is large. Within the Lungwena cohort, the study found little change in the relative bias of parameter estimates of the growth curve derived through MI between an imputation model that took account of the individual child's growth trajectory (longitudinal imputation model) and one that used population-level information at each given time point (cross-sectional imputation model). While Multiple Imputation is generally robust in handling missing data, care must be taken in defining an appropriate imputation model that best describes the relationship between the variable being imputed for and those used in the imputation. In longitudinal data, the imputation model has to take into account the longitudinal trajectory of the variable of interest.

The imputation model also has an effect on the performance of the Regression Imputation method. Despite regression imputation leading to increased power and precision of model parameter estimates due to increased number of observations, it is worth noting that the imputed values will be as good as the model used to do the imputation. If the growth model used fits well to the data, the regression imputed values will also be very close to the observed values or expected values (if the observed values are unknown).

7.4 LIMITATIONS

The main limitation of the study was the unavailability of common baseline and adolescent measurements for maternal and household characteristics in the two cohorts. This restricted the type of variables that could be added to the models during growth curve fitting in order to improve the fit of the curves. Studies have shown that maternal characteristics such as maternal height, maternal weight before pregnancy, maternal weight gain during pregnancy, as well as paternal characteristics such as height and weight, and general household socio-economic

status (derived from maternal and paternal education levels and other household factors) affect child growth (Flexeder et al., 2012, Menezes et al., 2012, Fraser et al., 2010, Young et al., 2012). This study was unable to fully account for these due to unavailability of some of the measurements in the Lungwena cohort. The absence of SES, pubertal stage and physical activity data in early adolescence for the Lungwena cohort was also a limitation in explaining the differences in the prevalence of adolescent obesity in the two cohorts.

7.5 RESEARCH GAPS AND FUTURE RESEARCH

The research gaps identified through this study have been divided into 2 components as outlined below. The methodological gaps relate to further research that can be done regards statistical methodology of modelling physical growth measurements and ways of handling missing data in such measurements. The empirical research gaps relate to further studies that could be done in relating early child growth and later health outcomes.

7.5.1 Methodology

In dealing with missing data, the current study only considered intermittent missing data. It would be of interest to consider the performance of these different methods in handling monotonic missing data (drop out). This could also be used to assess whether the performance of the methods would be affected by the time at which the drop out occurred. Would methods differ in their performance if drop out occurred early in the study (i.e. there is limited 'within individual' information and where the growth trajectory experiences rapid changes) or later on in the study (i.e. there is more 'within individual' information available for modelling process

early on)? Another line of enquiry would be to compare the performance of the methods under different missing data mechanisms (MAR, MCAR or MNAR) and with different amounts of missing data.

7.5.2 Empirical questions

In their study looking at the relationship between weight and height gain, and adolescent blood pressure and BMI, Menezes and colleagues (Menezes et al., 2012) found that rapid height gain without excess weight gain had beneficial long-term effects on blood pressure and BMI. However, they also recommended further studies to confirm their results. Our study looked at the relationship between rapid weight/height gain and early adolescent obesity (BMI) separately (in other words, the effect of weight gain did not take into account changes in height, and vice versa). It would be interesting to see if adjusting the two measurements for each other would produce results that are consistent to those found by Menezes and colleagues.

Since it is common practice in child growth monitoring in LMICs to promote weight gain in order to prevent the detrimental effects of under-nutrition, confirmation of results on the effect of adjusting for height gain would provide evidence for any recommendations in policy change regards child growth monitoring.

CHAPTER 8: CONCLUSIONS AND RECOMMENDATIONS

This chapter gives a summary of the thesis recommendations and proposes future related research issues that need to be addressed and gives overall methodological and empirical conclusions of the thesis.

8.1 CONCLUSIONS

Methodologically, in modelling physical growth measurements or any other characteristic that follow a well-defined trajectory, it is not necessary to impute for intermittent missing data, especially if data collection waves are not far apart. However, it is crucial to use a model that describes the growth trajectory well. Techniques that use available data such as multi-level modelling, sufficiently deal with the problems of missing data and correlation of repeated measurements in longitudinal studies. The flexibility of multi-level models to use the actual measurement time as opposed to the scheduled measurement time (e.g. a planned 6month visit may take place before or after 6 months), helps in reducing measurement errors associated with the variations in data collection periods.

Empirically, as it is already common practice in low-income countries, it is important to promote rapid weight gain in order to prevent the short-term and long-term adverse effects of under-nutrition. However, lessons must also be learnt from other low- and middle-income countries that are undergoing rapid nutritional transition, on the long-term detrimental effects of rapid infant weight gain, especially considering that in most countries, there is co-existence of under-nutrition and over-nutrition.

8.2 RECOMMENDATIONS

- It is appropriate to use LME without MI or Regression Imputation if the motive for modelling is to describe the general population distributions. LME are easier to perform in all Statistical software packages and are robust under MAR assumptions.

- Multiple Imputation requires an appropriate definition of the imputation model, which might not be as straight forward in some software packages.

- MI and Interpolation can be used if the motivation is to populate for missing data, so that other statistical methods that require complete data can then be applied. For example, in examining the relationship between early growth and later health outcomes, studies have used change in weight/height standard deviation scores (SDS) or conditional regression. The existence of missing data thus poses major challenges to the methods, since calculation of SDS is only possible if data exists at both data points.

- Common variables collected in longitudinal child growth studies in Low and Middle Income countries would aid comparability of populations, as well as learning from each other. This would also lead to a common evidence-based approach in dealing with co-existence of over and under-nutrition in LMICs.

- A common data repository to help countries do comparative studies on child growth and its effect on later adult health outcomes would be desirable especially to pool the scarce data in low and middle income countries. However, it has to be acknowledged that there may be challenges regards measurement and standardisation of life-course exposure variables.

- National longitudinal studies should also take into account lifestyle disparities between rural and urban settings. Most low income countries have concentrated their

programmes on dealing with under nutrition. Studies have indeed proposed that the short-term and long-term benefits of rapid weight gain in poor resource settings outweigh the long-term adverse effects. However, with most LMICs undergoing nutritional transition, the co-existence of over-nutrition and under-nutrition needs to be taken into account. It would be prudent under the changing circumstances to consider the detrimental long-term effects of rapid infant growth, and have programmes that raise awareness of the emerging health problem.

- Future studies in African settings should consider monitoring child growth from the fetal stage. This might be expensive but data from such studies will provide crucial information for this particular setting in terms of effect of impaired intra-uterine growth and increased risks of metabolic diseases in later life. Most studies have tended to use birth-weight as a proxy measure of fetal growth. However, it must be acknowledged that this measure is not very precise since different fetal growth patterns may in the end lead to similar birth weight. As suggested by Mook-Kanamori et al. (2011), studies that seek to understand the relationship between birth size and later life outcomes need to take into account fetal and infant growth measures.

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